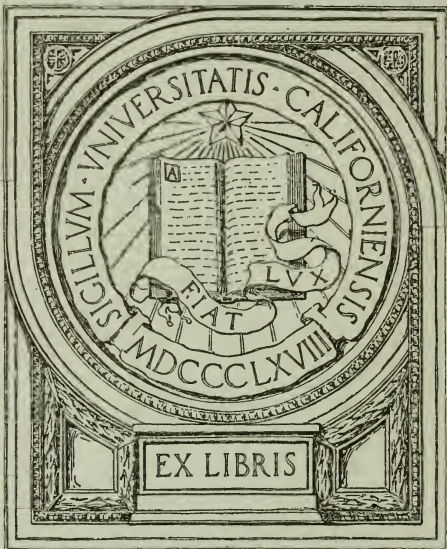


**NEW AND  
NONOFFICIAL  
REMEDIES**



1918

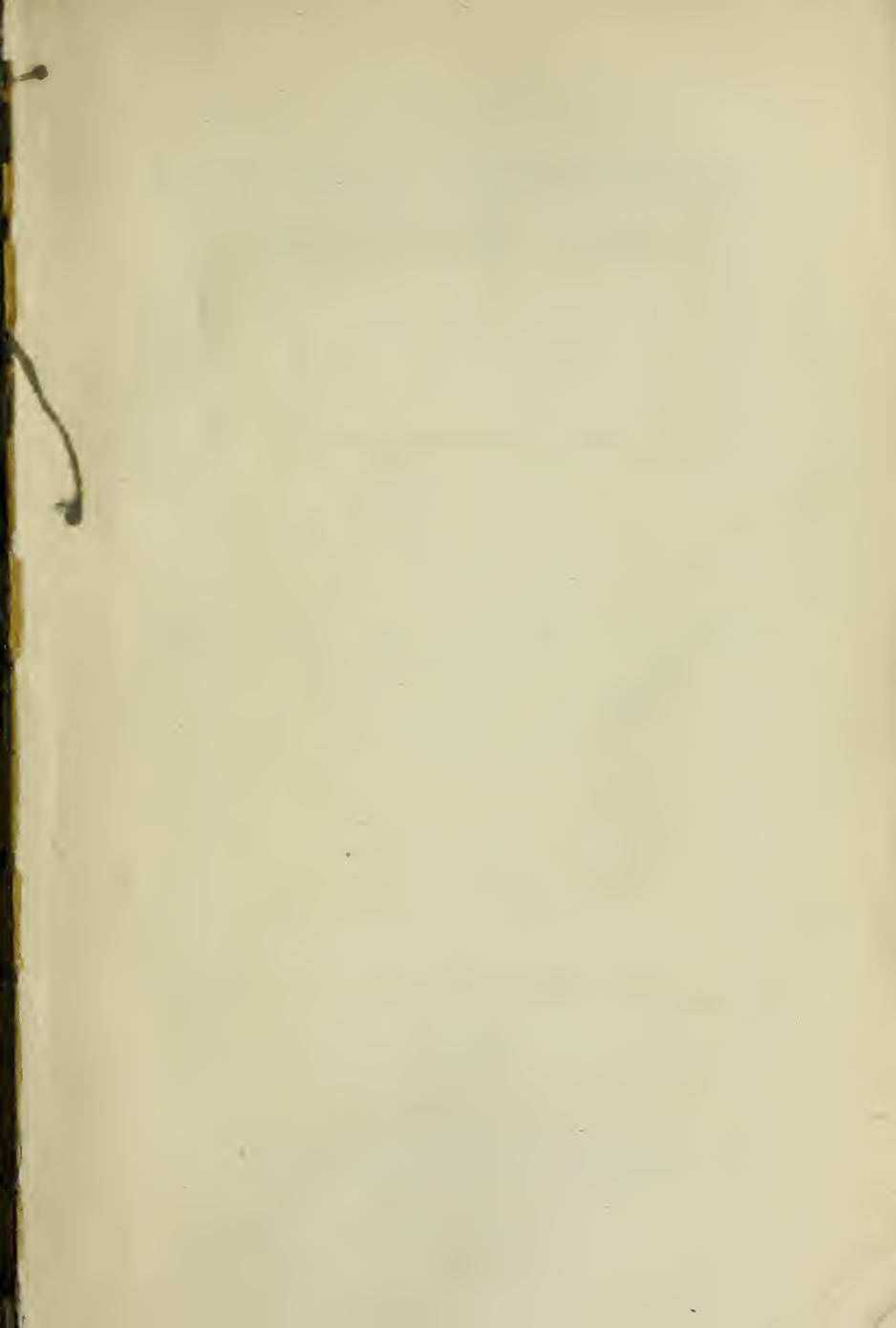
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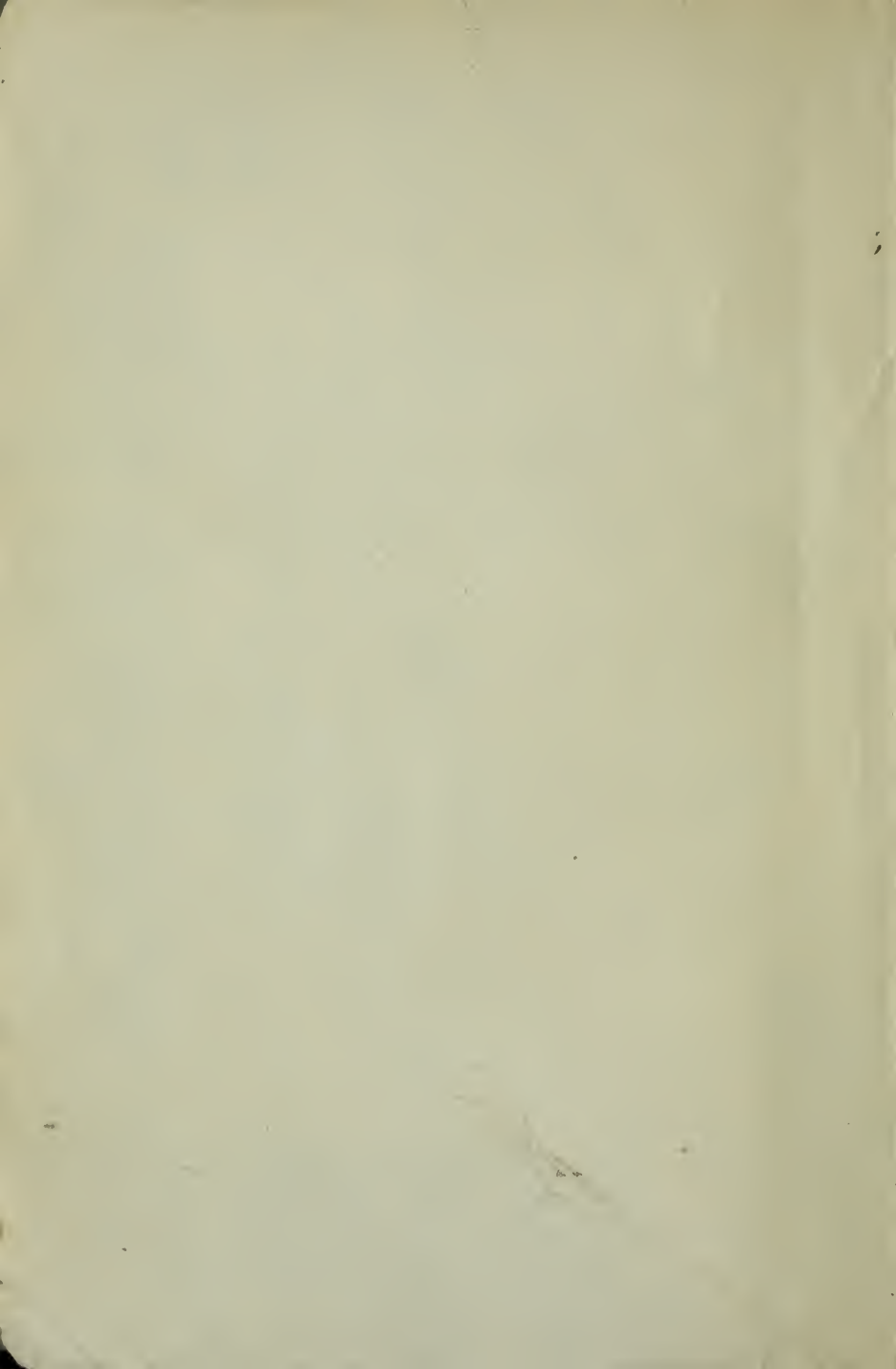


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# NEW AND NONOFFICIAL REMEDIES, 1919

Containing Descriptions of the

Articles Which Stand Accepted by the Council  
on Pharmacy and Chemistry of the  
American Medical Association  
on January 1, 1919

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CHICAGO  
AMERICAN MEDICAL ASSOCIATION  
FIVE HUNDRED AND THIRTY-FIVE NORTH DEARBORN STREET  
1919

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THAK TO VIM!  
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## P R E F A C E

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New and Nonofficial Remedies is a book in which are listed and described the articles that stand accepted by the Council on Pharmacy and Chemistry of the American Medical Association on January 1 of the year of publication. The descriptions of accepted articles are based in part on investigations made by or under the direction of the Council and in part on evidence or information supplied by the manufacturer or his agents. Statements made by those commercially interested are examined critically, and are admitted only when they are supported by other evidence or conform to known facts.

Articles which are included in the U. S. Pharmacopeia are not admitted to New and Nonofficial Remedies except in those instances in which proprietary preparations closely approaching U. S. P. products present improvements over the official article. However, when brands of articles now in the pharmacopeia were admitted to New and Nonofficial Remedies prior to the pharmacopeial recognition of such articles or where, because of such inclusion of brands, other brands of the same article were subsequently admitted, these are retained and grouped under the pharmacopeial title and reference made to the pharmacopeia for description; in some cases a statement of actions, uses and dosage has been retained.

The Federal Trade Commission having adopted the term Arsphenamine for 3-diamino-4-dihydroxy-1-arsenobenzene hydrochloride, the Council adopted this name for New and Nonofficial Remedies. Further, in accordance with the action of the Federal Trade Commission, New and Nonofficial Remedies recognizes the name Neoarsphenamine as the official designation for the product first introduced as neosalvarsan, and in like manner, Barbitol as the official name for the product first introduced as veronal, Barbitol Sodium in place of sodium diethylbarbiturate, Phenobarbital as the official name for the product first introduced as luminal, Phenobarbital Sodium as the official name for the product first introduced as luminal-sodium and Procaine and Procaine Nitrate, respectively, for the products first known as novocaine and novocaine nitrate.

The following articles have been omitted because they were found to be in conflict with the rules of the Council: Antithyroidin-Moebius; Arhovin; Bismuth Tribromphenate-Merck; Capsules of Bile Salts, Succinate of Soda and Phenol-

phthalein-Fairchild; Capsules of Holadin, Bile Salts and Phenolphthalein-Fairchild; Capsules of Holadin, Succinate of Soda and Bile Salts-Fairchild; Cephaeline; Colalin; Desiccated Pineal Gland-Armour, Desiccated Thymus-Armour; Empyroform; Extract of Red Bone-Marrow-Armour; Granular Effervescent Bromide and Acetanilid Compound-Mulford; Hemaboloids; Holadin and Bile Salts-Fairchild; Liquor Santaiva; Lycetol; Maltzyme; Maltzyme Ferrated; Maltzyme with Cascara Sagrada; Maltzyme with Cod Liver Oil; Maltzyme with Yerba Santa; Methaform; Pineal Gland; Piperazine; Pyocyaneus Bacillus Vaccine; Red Bone-Marrow; Soamin; Sodium Oleate; Tablets Acet-Phenetidin Compound-P. M. Co.; Thymus Gland; Thyroidectin; Xeroform-Heyden. The reports of the Council on Pharmacy and Chemistry should be consulted for the actions leading to the omission of articles.

The Council has omitted all those articles which at the present time are off the market. This has included a considerable number of products originating in countries with which the United States was at war and the importation of which, therefore, became illegal. The latter deletions account for the reduced size of the present edition.

In some instances the general discussions have been revised or rewritten. Attention is called to the revision of the article on digestive ferments; to the description of chlorinated eucalyptol; to the replacement of the monograph for neutral solution of chlorinated soda by one for surgical solution of chlorinated soda; to the discussion of sulphoichthyolate preparations; to the revision of the general and the special discussions of serums and vaccines; and to the article on silver preparations.

Some revision has been made in the statement of the actions, uses and dosage of procaine, arsphenamine, neoarsphenamine, herberine hydrochloride, crystallized ouabain, dimazon, tyramine hydrochloride, amphotropin, chloramine-T, dichloramine-T, spirosal, scarlet R medicinal-Biebrich, albargin, sulphanilic acid, soloid nizin, tannigen, and urea.

Revisions have been made in the standards of identity and purity or the statement of physical and chemical properties, or both, of the following substances: procaine, arsphenamine, neoarsphenamine, barium sulphate, bismuth tribromphenate, barbital, digitoxin, dichloramine-T, ovoferrin, atophan, cargentos, and arlco-urease.

During the year 1919 descriptions of such other medicinal substances as shall be accepted by the Council for "New and Nonofficial Remedies" will be published from time to time in THE JOURNAL, and will also be issued in the form of supplements, which will be sent to those who purchase this book.

W. A. PUCKNER, Secretary.

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# OFFICIAL RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY

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## INTRODUCTION

**OBJECT OF THE RULES.**—The following rules have been adopted by the Council with the object of protecting the medical profession and the public against fraud, undesirable secrecy and objectionable advertising in connection with proprietary medicinal articles.

**Contents of N. N. R.**—The book *New and Nonofficial Remedies* contains a description of proprietary articles which have been accepted as conforming with the rules of the Council; and of such simple nonproprietary and unofficial substances as seem of sufficient importance.

**Attitude on Mixtures.**—For admission to *N. N. R.* proprietary pharmaceutical mixtures must comply with the rules and to determine such compliance they will be investigated by the Council. The Council, however, endorses the principle that prescriptions should be written on the basis of the therapeutic effects of the individual ingredients. For this reason, it does not include in this book mixtures unless they present some real advantage. The physician who wishes to prescribe ready-made proprietary mixtures will find in the appendix to this book, listed under the name of the manufacturer, those proprietary mixtures which on examination have not been found to conflict with the rules.

**Nonproprietary Mixtures.**—Mixtures of nonproprietary substances are regarded as nonproprietary, and therefore are not contained in the book.

## RULES GOVERNING THE ADMISSION OF PROPRIETARY ARTICLES TO THE BOOK NEW AND NONOFFICIAL REMEDIES

**DEFINITION OF PROPRIETARY ARTICLES.**—The term, "proprietary article," in this place shall mean any chemical, drug or similar preparation used in the treatment of diseases, if such article is protected against free competition, as to name, product, composition or process of manufacture by secrecy, patent, copyright, or in any other manner.

**Rule 1.**—**COMPOSITION.**—No article will be accepted for inclusion in the book *New and Nonofficial Remedies* or retained therein unless its composition be furnished to the Council for publication. For simple substances the scientific name and the chemical formula, rational or structural if known, should be supplied. For mixtures the amount of each active medicinal ingredient in a given quantity of the article must be stated. The general composition of the vehicle, its alcoholic percentage, and the identity of the preservatives, must be furnished.



*Rule 2.—IDENTIFICATION.*—No article will be accepted or retained unless suitable tests for determining its composition are furnished to the Council. In the case of chemical compounds these shall consist of tests for identity and purity. In the case of mixtures, methods shall be furnished for determining the amount and active strength of the potent ingredients if practicable.

*Rule 3.—DIRECT ADVERTISING.*—No article that is advertised to the public will be accepted or retained; but this rule shall not apply: (a) to disinfectants, germicides and antiseptics, provided that the advertising be limited to conservative recommendations for their use as prophylactic applications to superficial cuts and abrasions of the skin and to the mucous surfaces of the mouth, pharynx and nose (but not to those of the eye, and the gastro-intestinal and genito-urinary tracts) and provided they are not advertised as curative agents (see comments to Rule 3); (b) to nonmedicinal food preparations, except when advertised in an objectionable manner.

*Rule 4.—INDIRECT ADVERTISING.*—No article will be accepted or retained if the label, package or circular accompanying the package contains the names of diseases in the treatment of which the article is said to be indicated. The therapeutic indications, properties and doses may be stated. (This rule shall not apply to remedies with which self-medication is altogether improbable, to vaccines and antitoxins, or to directions for administering or applying remedies where similar immediate, heroic treatment is indicated.)

*Rule 5.—FALSE CLAIMS AS TO ORIGIN.*—No article will be accepted or retained concerning which the manufacturer or his agents make false or misleading statements as to source, raw material from which made, or method of collection or preparation.

*Rule 6.—UNWARRANTED THERAPEUTIC CLAIMS.*—No article will be accepted or retained concerning which the manufacturer or his agents make unwarranted, exaggerated or misleading statements as to the therapeutic value.

*Rule 7.—POISONOUS SUBSTANCES.*—The principal label on an article containing "poisonous" or "potent" substances must state plainly the amount of each of such ingredients in a given quantity of the product.

*Rule 8.—OBJECTIONABLE NAMES.*—If the trade name of an article is not sufficiently descriptive of its chemical composition or pharmaceutical character, or is, for any other reason, unsatisfactory or objectionable, the Council reserves

the right to include with the trade name a descriptive title in the book. Articles bearing objectionably suggestive names will be refused consideration. Names which suggest diseases, pathologic conditions or therapeutic indications will not be admitted. (This limitation will not apply to vaccines, serums, antitoxins or foods.) In the case of pharmaceutical preparations or mixtures the trade name must be so framed as to indicate the most potent ingredients.

*Rule 9.—PATENTED PRODUCTS AND PROTECTED NAMES.*—If the article is patented—either process or product, or both—the number of such patent or patents must be furnished to the Council. Furthermore, if the name of an article is registered, or the label copyrighted, the registration (trademark) number and a copy of the protected label should be furnished the Council. In case of registration in foreign countries the name under which the article is registered should be supplied.

*Rule 10.—UNSCIENTIFIC AND USELESS ARTICLES.*—No article will be accepted or retained which, because of its unscientific composition, is useless or inimical to the best interests of the public or of the medical profession.

#### EXPLANATORY COMMENTS ON THE RULES

*INTRODUCTION.—History, Purpose, and Method.*—The Council on Pharmacy and Chemistry was established in February, 1905, by the American Medical Association, primarily for the purpose of gathering and disseminating such information as will protect the medical profession in the prescribing of proprietary medicinal articles. In pursuance of this object the Council examines the articles on the market as to their compliance with definite rules designed to prevent fraud, undesirable secrecy and the abuses which arise from advertising directly or indirectly to the laity. Such articles as appear to conform to the rules are accepted and their essential features are described in the annual publication of the Council, *New and Nonofficial Remedies*, if they come within the scope of this book.

*Submitted Evidence.*—These descriptions are based in part on investigations made by or under the direction of the Council, but in part also on evidence or information supplied by the manufacturer or his agents. Such interested statements are examined critically, and are admitted only if they appear to be in conformity with the evidence. It is, however, manifestly impossible for the Council to investigate the composition of every complex pharmaceutical mixture, or to check thoroughly every therapeutic claim; it can give only an unbiased judgment on the available evidence. Criticisms and

corrections of the descriptions which may aid in the revision of the matter will be appreciated.

*Previous Noncompliance and Fraud.*—The Council judges an article entirely by the facts in evidence at the time of its admission. Previous noncompliance with the rules (short of *intentional* fraud) does not prevent the favorable consideration of an article which is in accord with existing rules.

*Reconsideration.*—Infringements of the rules after acceptance of an article for New and Nonofficial Remedies, or the discovery that the Council's information was incorrect, will cause the acceptance to be reconsidered. An article is accepted for New and Nonofficial Remedies, and will continue to be included in the book, with the understanding that serious violations of the rules, after acceptance, will be followed by the omission of the article and publication of the reasons for such omission.

*Acceptance Not an Indorsement.*—The Council desires physicians to understand that the admission of an article does not imply a recommendation. Acceptance simply means that no conflict with the rules has been found by the Council.

**DURATION OF ACCEPTANCE.**—Unless an agreement to the contrary is made at the time of acceptance articles admitted to New and Nonofficial Remedies will be retained for a period of three years, provided that during that period they comply with the rules and regulations which were in force at the time of their acceptance. At the end of this period all articles will be carefully reexamined for compliance with existing rules. The reacceptance of articles after such reexamination shall be for three years unless a shorter period is specified.

Any amendments to the rules, by specific requirements or by interpretation, which may be made after the acceptance of an article, shall not apply to such article until the period of acceptance has elapsed. At the end of this period the article, if it is not eligible under the amended rules, will be omitted.

**THE SCOPE OF NEW AND NONOFFICIAL REMEDIES AND APPENDIX.**—To aid physicians and manufacturers in deciding what articles come within the scope of this book, or, in other words, to enable physicians to recognize whether an article has been omitted because it does not need admission or because it has been rejected, the Council furnishes the following more detailed definitions:

**OFFICIAL ARTICLES.**—Articles which are official in the United States Pharmacopeia or in the National Formulary are not considered by the Council since authoritative information concerning them is readily obtainable from another source.

*Nomenclature.*—To avoid confusion with nonofficial substances marketed under similar names the Council recommends that official substances be prescribed by their official titles, followed by the abbreviation, "U. S. P." or "N. F.," thus: Tincture Nucis Vomicae U. S. P., Elixir Gentianæ, N. F.

**SUBSTANCES DESCRIBED IN NEW AND NONOFFICIAL REMEDIES.**—In the body of the book will be described simple proprietary substances and their preparations if these be marketed by the original manufacturer; proprietary mixtures if they have originality or other important qualities which, in the judgment of the Council, entitle them to such place; and important nonproprietary unofficial articles.

*Suffix N. N. R.*—The Council recommends that when these latter are prescribed, they be indicated by the abbreviation, "N. N. R." thus insuring to the prescriber the quality of these articles laid down in the book.

**PROPRIETARY MIXTURES.**—*Definition.*—A mixture will be considered as proprietary, and therefore requiring consideration by the Council for admission to the book or appendix, if it contains any proprietary article; if it is marketed under a name which is in any way protected; or if its manufacturer claims for it any unusual therapeutic qualities.

*Where Listed.*—Proprietary mixtures which are marketed in conformity with the rules are listed in the appendix of the book under the names of the respective manufacturers. Such proprietary mixtures are not admitted to the body of the book, save in the exceptional cases cited in the preceding paragraph.

**NONPROPRIETARY MIXTURES OF OFFICIAL SUBSTANCES.**—Since the ingredients of such mixtures do not require consideration by the Council, and since the mixtures are not open to the proprietary abuses which called for the work of the Council, it is not necessary that they should be investigated by the Council. The physician must judge whether such mixtures should be directed to be prepared by the pharmacist, or whether he is justified in ordering a ready-made preparation. If he decides to use a ready-made nonproprietary preparation he must judge for himself if it is marketed in accordance with the rules.

*Trade Names.*—It should, however, be remembered that the application of a trade name to any substance makes it proprietary.

*Rule 1.*—**COMPOSITION.**—*Secrecy Objectionable.*—It is not only the right but also the duty of the physician to know the



essential composition of what he prescribes; the Council cannot compromise on this proposition.

*Vehicles and Preservatives.*—In the case of mixtures not only the potent ingredient, but also the general character of the vehicle, the presence of alcohol, and the identity of preservatives, or of any other substance, whether added or present as an impurity, must be stated, if these can under any circumstances affect the therapeutic action of the article. This, as a rule, does not mean the publication of trade secrets, such as flavors or the details of the working formula.

*Trade Secrets.*—Furthermore, trade secrets will not be received as confidential by the Council, since it accepts information only with the distinct understanding that this may be freely published, at its discretion.

*Inspection of Factories.*—The Council does not accept invitations to inspect factories; its concern is with the finished products.

On the other hand, the Council requires that the information be complete and accurate as to medicinal ingredients.

*Unofficial Constituents.*—Unofficial constituents of proprietary mixtures must be presented by the manufacturer in the regular way and must be acted on by the Council before the preparations containing them can be accepted.

*Fraud.*—When it appears that a manufacturer has made a *deliberately* false statement concerning a product he is asked to furnish an explanation; and if this is not satisfactory the product will not be accepted, even if the false statement is subsequently corrected or omitted.

*Testimonials.*—This applies not only to statements made to the Council, but also to statements furnished to physicians by the manufacturer or his agents, even when these statements are in the guise of testimonials.

*Rule 2.—IDENTIFICATION.*—In order to avoid errors in the case of chemical compounds, and to guard against adulterations, lack of potency or strength and the mistaking of one chemical for another, it is necessary to have at hand suitable tests.

*Tests, etc.*—If these facts have appeared in the literature, or in standard textbooks, reference to them will be sufficient; but with new chemicals, especially synthetics, the manufacturer or his representatives will be required to supply such tests for publication, in order that an intelligent opinion of these products may be assured.

*Physiologic Standardization.*—In cases in which chemical methods of identification are unknown or unreliable, physio-

logic standardization should be employed. The Council considers the phrase "Physiologically standardized" or "assayed" as misleading unless the standard and method are published in sufficient detail to permit of their control by independent investigators.

It is evident that when no standard is published, it is impossible to know whether the quality is high or low, and the conscientious manufacturer who sets for himself a high standard is placed on a level with the dishonest or careless one who adopts a low standard. Again, if the process of standardization is not published, it is impossible to learn without actual trial the relative value of one preparation as compared with that of another manufacturer or to confirm or disprove the statements of the manufacturer as to the quality of his product.

*Standardization of Disinfectants and Germicides.*—No disinfectant or germicide of the phenol type will be accepted for N.N.R. whose phenol coefficient, determined according to the method of the Hygienic Laboratory, U.S.P.H.S., is not stated on the label of the preparation.

*Rule 3. — DIRECT ADVERTISING. — Lay Advertising.*—The impossibility of controlling the irresponsible claims which are usually made in advertisements to the public, the well-known dangers of suggesting by descriptions of symptoms to the minds of the people that they are suffering from the many diseases described, the dangers of the unconscious and innocent formation of a drug habit, and the evils of harmful self-medication, including the dangers of the spread of many infections and contagious diseases when hidden from the physician, and similar well-known considerations, are the reasons for discouraging, in the interest, and for the safety, of the public, this reprehensible form of exploitation. Advertising in medical journals, etc., distributed solely to physicians, does not come within the scope of this rule.

*Exceptions.*—In the case of subjects on which the public should be instructed, as the use of disinfectants, germicides, antiseptics and foods, advertisements to the public, if not in objectionable forms, are considered admissible.

In no case shall such advertisements include recommendations for use as curative agents, nor shall the names of any diseases be mentioned in exploitation. If the preparation is sufficiently toxic to require caution in its use to prevent poisoning, this fact shall be stated on the label. On account of the deplorable results which would follow any abuse of this privilege, the conscientious cooperation of manufacturers and their agents in adhering strictly to the limitations laid

down is asked; and for the same reason the acceptance of an article which is so advertised as to infringe on these limitations in any essential way (as by naming diseases or by making false and exaggerated claims) shall be summarily rescinded, and the reasons for such action may be published without notice to manufacturer or agent. A disinfectant, germicide or antiseptic will be accepted for description in New and Nonofficial Remedies, and an article of this class which has already been accepted will continue to be included with New and Nonofficial Remedies only on the explicit understanding by the manufacturer and agent that such infringements of the rule will be followed by deletion of the article and by publication of the facts as described.

*Foods.*—We may divide the foods into three groups. The first group contains the ordinary foods, including the well-known breakfast foods. These do not come under the supervision of the Council in any way. The second group includes a large and important class of manufactured products, such as invalid and infant foods, which in a sense stand between the first and third groups. The public has the same interest in these foods that the physician has, and usually is supplied with full information concerning them. While the primary recommendation of these articles should naturally come from the physician, it cannot be expected that their continued use should depend on repeated prescriptions. Information concerning this group of foods would come naturally and properly from a physician, and the collection and dissemination of this information may very properly be included in the work of this Council. As the products in this class are used extensively, it is not proper to limit their advertising to medical journals, but the advertising should be permitted in the lay press so long as it is conducted in a manner compatible with the rules of the Council. The third group includes medicinal foods proper, such as predigested foods. These have a relatively low food value and are characterized by a high alcohol or preservative content. They frequently contain strictly medicinal substances, or food substances for which distinct therapeutic properties are claimed. These products should be used only on the advice of the physician, and the advertisement should be restricted as in the case of ordinary medicines.

*Advertisements in Foreign Countries.*—The Council deals primarily, in the interest of the public and of the medical profession, with articles proposed for admission to New and Nonofficial Remedies, and, in determining the status of any article, must take into consideration any statements made



regarding it or any method of advertising it employed by the manufacturer or his authorized agents or representatives, whether in this country or abroad. The Council will not regard as within its scope, however, questions concerning the marketing of articles (except the matter of direct advertising to the laity and unwarranted claims or misrepresentations) in any country which has a public body corresponding to this Council.

*Rule 4.—INDIRECT ADVERTISING.*—It should be remembered that the sole intent of this rule is to protect the physician, so that in prescribing a proprietary medicine he shall not unconsciously advertise proprietary preparations. The rule imposes no restriction on the legitimate methods of bringing a remedy to the attention of the profession, such as advertising in medical journals, circulars and other printed matter distributed solely to physicians. The rule applies only to the package as it may reach the patient.

*Naming Diseases on Label.*—The naming of diseases on the label or package is not necessary, as is shown by the very large number of proprietary products which have been successfully introduced without resorting to this expedient. This method of popularizing a proprietary remedy with the laity is most objectionable, and should not be tolerated in any form.

*Therapeutically Suggestive Names.*—The Council considers therapeutically suggestive names (see Rule 8) as an unworthy expedient to the same end. It would prefer to have therapeutic indications omitted from the label and package, but does not insist on this point, because these are useful in some exceptional cases.

*Permanently Affixed Names.*—It will be considered an infringement of the rule if an article be marketed in bottles which have the name of the article blown into the glass, or if otherwise the name or initials or other distinctive mark of the article are permanently stamped on the container, on the article itself, or are on the stoppers or seals. Articles which are marketed in any of these ways are not accepted for New and Nonofficial Remedies. Readily removable labels are not objectionable nor is the permanent affixing of the firm's initials or name to the trade package if such initials or name be not suggestive of the article.

*Use of Articles for Advertising.*—The Council does not countenance the use of an accepted article for advertising other articles which have not been accepted by the Council.

*Rule 5.—FALSE CLAIMS AS TO ORIGIN.*—No false or misleading statement in regard to an article can be permitted concerning the source or material from which it is made, or the persons by whom it is made. Some glaring frauds of this nature have been perpetrated in the past, and this rule is intended to prevent such imposition.

*Rule 6.—UNWARRANTED THERAPEUTIC CLAIMS.*—This rule insists that the claims of manufacturers or agents concerning the therapeutic properties of their products must be compatible with demonstrable facts. Manufacturers will be held responsible for all statements made or quoted in their advertising literature regarding their products. Recognizing the existence of honest differences of opinion on many therapeutic questions, the Council desires to be liberal in the application of this rule. It is natural that a manufacturer should be partial toward his own product, and a moderate degree of emphasis in advertising may not be objectionable. The Council, however, will not admit claims which are neither in harmony with already accepted facts nor supported by acceptable evidence. In doubtful cases the Council considers these questions with the advice and cooperation of its staff of clinical consultants.

*Clinical Evidence.*—To be acceptable, the clinical evidence must offer objective data with such citation of authority as will enable the Council to confirm the facts and establish the scientific value of the conclusions drawn. Clinical data are worthless when the author is not cited. The facts on which claims with regard to the value of a remedy are based must have been rendered accessible for investigation and confirmation by disinterested observers, either through publication or through the records of a hospital or other institution.

*Rule 7.—POISONOUS SUBSTANCES.*—For the information of the pharmacist or dispenser, and to enable him to safeguard the interests of the patient and the physician, all articles containing such potent agents as the poisonous alkaloids and other organic substances and the salts of some of the metals, should have the exact amount of these ingredients which is contained in the average adult dose stated on the label.

*Rule 8.—OBJECTIONABLE NAMES.*—Many of the abuses connected with proprietary medicines are intimately associated with the more or less arbitrarily selected or "coined," usually protected, names.

*Scientific Names.*—In the interest of those physicians who would prefer to employ a more rational nomenclature the Council recommends the adoption of scientific names by the

manufacturers, at least as synonyms. In view of the existing trade conditions, however, the Council does not insist on this except in such specific cases as are explained below in which experience has shown the necessity of restrictions.

*Objectionable Trade Names for Official Substances.*—The application of "trade names," protected or not, to official or established nonproprietary products tends to confusion and fosters many abuses. Such trade names will therefore not be recognized by the Council unless they antedate the recognition of the article in the United States Pharmacopeia, National Formulary or New and Nonofficial Remedies.

*Use of Firm Names.*—The protection of the manufacturer can be amply secured by appending the firm or "brand" name to the official name, and to this there can be no objection. Appended names or initials of manufacturers as in *Mistura Rhei et Sodæ*, X. Y. & Co.; *Mixture of Rhubarb and Soda*, "Jones"; *Pills of Aloes and Iron*, "Smith brand," are considered nonproprietary.

*Generic Names.*—Protected generic brand names shall not be regarded as proprietary. Any preparation containing a proprietary article, however, in virtue of this is also a proprietary.

*Pharmaceutical Preparations and Mixtures.*—Since these, with rare exceptions, are not original in composition, there is no sufficient reason why they should be endowed with arbitrary names; on the contrary, it is important that the prescribing physician should be constantly reminded of the potent ingredients on which the actions of such preparations are based. It is particularly important that actively poisonous or habit-forming drugs be not disguised under an innocently worded title.

Nonessential modifications of official or nonproprietary preparations will not be recognized. Essential and important modifications, however, will be accepted and described in New and Nonofficial Remedies.

*Coined Names, Where Permitted.*—The Council recognizes, on the other hand, the right of discoverers of new synthetic products or active principles to name their discoveries, and interposes no objection to arbitrary names for such products, so long as such names do not suggest a therapeutic use. It is desirable, however, that the coined name should indicate at least the chief potent ingredient or ingredients. With a definite chemical substance, in addition to the trade name a descriptive chemical name should appear on the label, and in advertisements and circulars; and if such chemical substance is official in the U. S. P. the pharmacopeial name should also be given. (However, the Council interposes no objections to the use of labels or circulars already printed provided that these are used prior to Jan. 1, 1919, and provided also that this rule will not be enforced when the size or character of the label or circular makes the use of the chemical name or pharmacopeial synonym infeasible.)

*Therapeutically Suggestive Names.*—Articles whose names suggest therapeutic uses will not be accepted for New and Nonofficial Remedies. They are objectionable, first, because they are likely to lead the thoughtless physician into prescribing *names* instead of *remedies*. This objection applies, although the name may have little or no meaning to the layman. They are objectionable, secondly, because they tend to encourage self-medication by the laity. Even if the name be at first comparatively meaningless to the public, its meaning will soon be understood when it is used by physicians. Patients soon learn the technical terms applied to their disease and its symptoms.

The objection to therapeutically suggestive names does not apply to vaccines, serums and antitoxins, because the specific character of these remedies must be preserved in their names in order to avoid confusion and mistakes in medication, and because self-medication with these remedies is altogether improbable. Foods are also excepted because they will only be used after a proper diagnosis has been made.

*Removal of Conflict with Rule 8.*—If an article conflicts only with Rule 8, it may be admitted as soon as the manufacturer substitutes a name which the Council considers satisfactory.

*Rule 9.*—PATENTS, TRADEMARKS, COPYRIGHTS, ETC.—This information is important as a means of determining the legal status of medicinal articles and as an aid to their ready recognition in current publications.

*Rule 10.*—UNSCIENTIFIC AND USELESS ARTICLES.—The use of articles which are unessential modifications of official or established nonproprietary articles is unscientific and serves no useful purpose. The Council will not accept products which are scientifically unsound and which, therefore, must be considered useless or inimical to the best interest of the medical profession and the public. This class includes compounds or mixtures containing an excessive number of active ingredients; those compounds or mixtures the components of which are of no probable assistance to each other and those articles which are of no therapeutic value. The combination of two or more active components in a compound or of two or more active ingredients in a mixture must be considered contrary to rational medicine unless a distinct reason exists for such combination. Such compounds or mixtures containing two or more active ingredients will be held in conflict with Rule 10 unless satisfactory evidence to warrant the combination is presented.

UNESSENTIAL MODIFICATIONS OF OFFICIAL SUBSTANCES.—  
*Imitations.*—The subterfuge of obtaining proprietary rights over an official or established nonproprietary product, by introducing unessential modifications, also tends to confusion and abuses, and such articles will not be admitted by the Council. Essential and important modifications, however, will receive recognition. (The Council interprets the term “established nonproprietary product” to apply to a preparation of any formula which has been published through any recognized or reasonably accessible channel of publication, prior to its appropriation or modification by a manufacturer.)



# NEW AND NONOFFICIAL REMEDIES

## AGAR AND AGAR PREPARATIONS

**AGAR.**—Agar-Agar.—For description see the U. S. Pharmacopeia under Agar.

**Agar-Agar-Merck.**—Agar supplied in the form of powder and shreds (see below).

Merck & Co., New York, distributors.

*Agar-Agar Powder-Merck.*—Agar in the form of a coarse powder.

*Agar-Agar Shreds-Merck.*—Agar in the form of shreds.

**PHENOLPHTHALEIN-AGAR.**—Agar impregnated with phenolphthalein, 100 Gm. containing 3 Gm. of phenolphthalein.

*Actions and Uses.*—Phenolphthalein-agar is claimed to have the properties of agar augmented by the action of phenolphthalein.

*Dosage.*—1 Gm. (15 grains) twice daily, after breakfast and supper, increased or diminished according to requirements.

Manufactured by the Chemische Fabrik Helfenberg, A. G. Helfenberg, Saxony, Germany (Reinschild Chemical Co., New York). U. S. patent No. 943,163 (Dec. 14, 1909; expires 1926). No. U. S. trademark.

Phenolphthalein-agar is prepared by impregnating 1,000 Gm. of agar with a solution obtained by dissolving 30 Gm. of phenolphthalein in a mixture of 2,000 Cc. of water and 700 Cc. of alcohol and slowly drying the impregnated agar.

**AGARIC ACID.**—*Acidum Agaricum.*—*Acidum Agaricinicum.*—*Agaricinum.*—A tribasic acid,  $C_{10}H_{38}OH(COOH)_3 + 1\frac{1}{2}H_2O$ , derived from *Polyporus officinalis*, Fries (Order *Hymenomycetes*; fam. *Polyporeae*) a fungus growing on the European larch and other species of larch.

**NOTE.**—The substance commonly sold as agaricin is an impure alcoholic extract.

*Actions and Uses.*—Agaric acid is a local irritant and in large doses produces vomiting and purging, and death through central paralysis. It paralyzes the peripheral nerves of the sweat-glands, arresting the secretion of sweat. It is used to arrest colliquative sweats. The experience of most clinicians is favorable, but some report that they were unable to obtain any favorable effects. The action appears in a few hours and is not lasting. Agaric acid is one-twentieth as active as atropine and does not influence other secretions.

*Dosage.*—The maximal single dose of agaric acid should not exceed 0.03 Gm. ( $\frac{1}{2}$  grain) and the total daily dose should not exceed 0.1 Gm. ( $1\frac{1}{2}$  grains). Owing to its irritant action it cannot be given hypodermically.

Agaric acid occurs as an odorless, tasteless, glistening microcrystalline powder, which melts at from 141.5 to 142 C. When heated to a high temperature it is volatilized in the form of a white pungent vapor. Agaric acid is slightly soluble in cold water; when heated with from 50 to 100 parts of water it becomes gelatinous and finally dissolves to a weakly acid solution, which possesses the characteristic property of foaming strongly when shaken. The addition of acids to hot aqueous solutions of agaric acid causes white flocculent precipitate, but a tannic acid solution (1:100) produces neither coloration nor turbidity. With alkalis agaric acid forms water-soluble salts. Agaric acid is slightly soluble in ether, chloroform, carbon disulphide and in 130 parts 90 per cent. alcohol. It is soluble in hot acetic acid, acetic ether, oil of turpentine, and in about 10 parts of alcohol.

If to a mixture of about 0.2 Gm. of agaric acid with 3 Cc. of water 2 drops of alcoholic alphanaphthol solution (1.8) are added and then gradually 5 Cc. of concentrated sulphuric acid added the mixture should not take on a marked blue-violet color. If 0.1 Gm. agaric acid be boiled with 10 Cc. dilute sulphuric acid a turbid solution results, from which on standing on a water-bath oily drops separate, which crystallize on cooling. If 0.1 Gm. agaric acid be incinerated it should leave no weighable residue.

## ALUMINUM COMPOUNDS

Several of the compounds of aluminum are official, including the ordinary alum (alumen, U. S. P.). The acetate and the acetotartrate of aluminum (official in the National Formulary) are used in the form of solutions.

The aluminum compounds are used for their astringent action. Since they are but little absorbed, they are relatively non-toxic, although long-continued use may lead to slight symptoms of metal poisoning.

Compounds of aluminum are astringent because of their property of precipitating albumin. The exsiccated alum is more energetic, not only because it contains a larger proportion of alum than the crystalline, but also because it absorbs water from the tissue at the same time. The acetate is milder than the sulphate, as is usual with metallic salts.

The aluminum compounds are not so astringent as the corresponding lead salts, but they may exert an irritant and even caustic action when used in concentrated solutions or in the form of the "burnt" alum. When swallowed in overdoses in such concentrated form they may cause gastritis and diarrhea. Alum is sometimes used as an emetic.

The aluminum compounds are slightly antiseptic, a property which goes with their astringency. Some of the organic compounds are said to be more actively antiseptic than the inorganic.



Several proprietary preparations, consisting of aluminum combined with organic acids, have been introduced with a view to utilizing the astringent and antiseptic properties of their components. Many of these possess no special advantages and have fallen into disuse, or have been largely replaced by others of a more or less similar nature.

## ANESTHETICS

### Anesthetics, General

**ETHYL BROMIDE.**—Æthylis Bromidum.—Æther Bromatus.—Æthylum Bromatus.— $C_2H_5Br$ .—The hydrobromic acid ester of ethyl alcohol, containing approximately 1 per cent. ethyl alcohol.

*Actions and Uses.*—Ethyl bromide is a rapid anesthetic, acting much like chloroform. The anesthesia is quickly and pleasantly induced and the recovery is rapid, but subsequently the patient may have general mild depression. Pain is abolished before consciousness. The respiration is paralyzed at about the same time as the reflexes, so that the zone of safety is very narrow. Tetanic spasms have occurred. Deaths caused by this drug were formerly attributed to impurities, but several have occurred when a pure article was given. It has been recommended for short operations in obstetrics, gynecology and minor surgery, but is not to be used for long operations. It must be regarded as a very dangerous agent in inexperienced hands.

*Dosage.*—From 3 Cc. to 12 Cc. (45 minims to 3 fluidrachms) is sufficient to induce anesthesia. It should be administered rapidly with little or no air. The administration requires from twenty to forty seconds; the anesthesia lasts about two minutes. The dose for children should not exceed 1 Cc. for each year of age.

Ethyl bromide should be protected from the light, and a bottle when opened should be used at once, as it deteriorates rapidly. (To be preserved carefully in small, opaque bottle containing not more than 50 Cc.) It should not be confounded with ethylene bromide, which is said to be very poisonous. The specific gravity of ethylene bromide is 2.179, while that of ethyl bromide is about 1.45.

Ethyl bromide is a colorless, strongly refractive, easily volatile liquid, having a pleasant ethereal odor. It is insoluble in water, but readily soluble in alcohol and in ether. It boils at from 37 to 39 C. Its specific gravity at 15 C. is 1.453 to 1.457. It is stable when pure, but when contaminated with ethyl iodide it becomes colored on exposure to light. It burns with difficulty. It is with much difficulty saponified by potassium hydroxide and it is not attacked by sulphuric or nitric acids. Silver nitrate gradually precipitates silver bromide.

If a mixture of 1 Cc. ethyl bromide, 5 Cc. alcohol and 10 drops of (15 per cent.) sodium hydroxide solution is heated to boiling, cooled, acidified with dilute sulphuric acid, then shaken with chloro-

form and chlorine water added, a brown coloration will be produced in the chloroform layer. If equal volumes of ethyl bromide and sulphuric acid are shaken together in a bottle previously rinsed with sulphuric acid and closed with a glass stopper, the acid should not be colored yellow within an hour. After shaking equal volumes of ethyl bromide and water, no change of volume should occur in the two liquids, the water separated from the ethyl bromide should not have an acid reaction nor should it become turbid immediately on the addition of a drop of silver nitrate solution. When a small portion is evaporated from a porcelain plate by causing it to flow to and fro over the surface, little or no foreign odor is yielded as the last portions pass off, and the plate is covered with a slight deposit of moisture. One Cc. of ethyl bromide mixed with 3 drops of aniline and 2 Cc. of alcoholic solution of potassium hydroxide should not give off the odor of isonitrile even after warming (*chloroform*).

**Ethyl Bromide-Merck.**—A nonproprietary brand complying with the standards for ethyl bromide.

Merck & Co., New York, distributors.

**ETHYL CHLORIDE.**—For description see the U. S. Pharmacopeia under *Aethylis Chloridum*.

**Kelene.**—A name applied to ethyl chloride, U. S. P., supplied in a special form of container.

Manufactured by Fries Bros., New York (Merck & Co., New York).

**METHYL CHLORIDE.**—*Methyl Chloridum.*— $\text{CH}_3\text{Cl}$ .—The hydrochloric acid ester of methyl alcohol. It occurs, in the compressed state, as a colorless liquid, having an ethereal odor, and a sweet taste.

*Actions and Uses.*—By its evaporation a temperature of  $-23^\circ\text{C}$ . is produced, while if evaporation be accelerated by means of a current of air a temperature of  $-55^\circ\text{C}$ . may easily be reached. On account of this property its use requires caution, since it is apt to produce blisters. The diluted vapor is said to be non-poisonous. Methyl chloride is said to be an efficient general anesthetic, which has practically no influence on the circulation, but fails to produce complete muscular relaxation. It is used as a general anesthetic mixed with ethyl chloride and ethyl bromide.

*Dosage.*—When methyl chloride is sprayed on the skin the part should be somewhat protected by a thin layer of cotton wool. When the anesthetic is used locally, cotton wool soaked in liquid methyl chloride may be applied to the skin over the painful area, but care should be taken that blisters are not formed. In order to avoid this a mixture with ethyl chloride has been recommended.

Methyl chloride is insoluble in water, more readily soluble in alcohol, freely soluble in ether and chloroform, and also in acetic acid. It should be neutral to litmus paper. Pure methyl chloride has a

specific gravity of 0.99145 at  $-23.7^{\circ}\text{C}$ . It burns in air with a greenish flame, though it is not highly inflammable. The neutral solution is not precipitated by solution of silver nitrate, nor is there any reaction with potassium iodide and starch paste. In the liquid condition it is a powerful refrigerating agent. At very low temperatures it forms with water a hydrate,  $\text{CH}_3\text{Cl.9H}_2\text{O}$ . It should not react alkaline to litmus (*ammonia and methylated ammonia—methylamine*). It should not immediately form a precipitate with silver nitrate. On evaporating it should leave no residue and emit no odor of methylamine.

### Anesthetics, Local

There are three general groups of drugs used for the production of local anesthesia: (1) those which cause anesthesia through the production of cold, such as ether, ethyl chloride and methyl chloride; (2) certain protoplasmic poisons, as quinine; and (3) those having a specific effect on sensory nerves or their endings; cocaine is the type of this class.

The drugs listed below belong, in general, to the third class. They have been introduced with the object of finding substances less toxic and more stable and less injurious to the tissues than cocaine. Their anesthetic power is also as a rule somewhat less than that of cocaine and most of them present the usually undesirable effect of dilating the blood-vessels or at least of not constricting them as does cocaine; hence some of them are almost always employed in conjunction with epinephrin. They owe their origin to the discovery that local anesthetic action of cocaine is due to the radical of benzoic acid in combination with a nitrogen-containing basic group. The simplest of these compounds, anesthesin, propaesin and cycloform, are, respectively, ethyl, propyl and isobutyl esters of para-amino benzoic acid,  $\text{C}_6\text{H}_4(\text{NH}_2)\text{COOH}$ ; orthoform and orthoform-new are the methyl esters of oxy-amino benzoic acids,  $\text{C}_6\text{H}_3(\text{OH})(\text{NH}_2)(\text{COOH})$ . All of these are too weak or too insoluble in water to be useful for hypodermic injections; they are used as local applications. Procaine is a compound of para-amino-benzoic acid with diethyl-amino-ethyl alcohol; its salts are readily soluble in water. Stovaine and alpin are esters produced by combination of benzoic acid with derivatives of an amino-amyl alcohol; their salts are easily soluble in water, but they are much more toxic than the preceding compounds. Beta-eucaine is a compound of benzoic acid and derivative of oxypiperidin. Tropacocaine is much more closely related to cocaine than are the preceding.

*Cocaine Substitutes.*—The relative toxicity of the synthetic substitutes for cocaine, included in New and Nonofficial Remedies, are exhibited in the following table:

Anesthesin	Non-toxic
Propaesin	Practically non-toxic
Stovaine	From one-third to one-half as toxic as cocaine
Alypin	One-half as toxic as cocaine
Procaine	Less toxic than stovaine or alypin
Beta-eucaine hydrochloride	Much less poisonous than cocaine
Tropacocaine hydrochloride	One-half as toxic as cocaine

**ALYPIN.** —  $\text{CH}_3\text{CH}_2\text{C}(\text{C}_6\text{H}_5\text{COO})[\text{CH}_2\text{N}(\text{CH}_3)_2]\text{CH}_2\text{N}:(\text{CH}_3)_2\text{HCl}$ .—The hydrochloride of 2-benzoxy-2-dimethyl-amino-methyl-1-dimethyl-amino-butane. It is closely related to stovaine (which see).

*Actions and Uses.*—Alypin is a local anesthetic, claimed to be equal to cocaine, but is not a mydriatic. It is said not to produce disturbance of accommodation and to be less toxic than cocaine, but the evidence as to the relative toxicity of alypin and cocaine is rather conflicting. Death was reported in one case from the injection of about 7.4 Cc. of a 10 per cent. solution into the urethra and bladder; severe poisoning has resulted from smaller amounts.

*Dosage.*—Externally in the form of a 10 per cent. solution; hypodermically in 1 to 4 per cent. solution; for the eye in 1 to 2 per cent. solution. As much as 5 Cc. of a 3 per cent. solution was well tolerated in one case.

Alypin is sold in the form of tablets only (see below).

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent No. 808,748 (Jan. 2, 1906; expires 1923). U. S. trademark No. 44,608.

*Alypin Tablets, 1/3 grain.*—Each tablet contains 0.022 Gm. ( $\frac{1}{2}$  grain) of alypin.

By the action of dichloroacetone,  $\text{CH}_2\text{Cl.CO.CH}_2\text{Cl}$ , on ethylmagnesium bromide dissolved in ether and decomposition by water of the magnesium compound formed, ethyl-dichlorhydrin,  $\text{CH}_2\text{Cl.C}_2\text{H}_5(\text{OH}).\text{CH}_2\text{Cl}$ , is obtained. From this, by the action of dimethylamine, ethyl-tetramethyl-diamino-propanol is produced. This product is treated with benzoyl chloride and the benzoyl-ethyl-tetramethyl-diamino-propanol neutralized with hydrochloric acid to form the chloride.

Alypin is a white, crystalline powder, melting at 169 C., hygroscopic and extremely soluble in water. Its solutions are neutral and are not rendered turbid on addition of sodium bicarbonate in moderate quantities, and may be sterilized by boiling for a period not exceeding five minutes, without decomposition. It is easily soluble in alcohol. It has a markedly bitter taste. It should be protected from the air in well-stoppered containers. Two and 4 per cent. solutions are quite stable, but weaker solutions are likely to become moldy.

Addition of potassium iodide test solution to the aqueous solution (1:100) produces a white precipitate; potassium dichromate test solution produces a yellow crystalline precipitate soluble in hydrochloric acid; potassium permanganate test solution produces a violet crystal-



line precipitate, which turns brown on standing. If 0.1 Gm. alypin be mixed with 1 Cc. sulphuric acid and warmed to 100 C. for five minutes and then 2 Cc. water carefully added the odor of benzoic ethyl ether is developed; on cooling crystals separate out, which are dissolved on adding 2 Cc. alcohol. If alypin be dried at 100 C. the loss should not exceed 1.5 per cent.

**ANESTHESIN.**—*Æthylis Amino-Benzoes.*—Ethyl Amino-benzoate.—Paraminobenzoic Acid Ethyl Ester.— $C_6H_4.NH_2.COO(C_2H_5)$ .—The ethyl ester of 4-aminobenzoic acid,  $C_6H_4.NH_2.COOH$ .

*Actions and Uses.*—Anesthesin was introduced as a substitute for cocaine and is a local anesthetic, similar in its action to orthoform-new and to propaesin (propyl aminobenzoate), free from irritant action and toxicity. The anesthetic action, like that of the related compounds, resembles that of cocaine, but is purely local, not penetrating the mucous membranes, and in consequence of its insolubility the compound cannot be used by hypodermic injection. In consequence of its insolubility, also, the anesthetic effect is more prolonged than that of cocaine. It is sometimes injected intramuscularly with insoluble mercury compounds to diminish the pain.

It is said to be useful in various forms of gastralgia, in ulcer and cancer of the stomach, for the relief of pain, and is applied locally in rhinologic and laryngeal affections, urethritis, etc.; it is also employed for anesthetizing wounded surfaces, burns, ulcerations and painful affections of the skin. It is more effective in cases in which the skin is broken.

*Dosage.*—Internally, from 0.3 to 0.5 Gm. (5 to 8 grains). Externally, it is applied as a dusting powder, either pure or diluted. It may be applied in ointment or in the form of suppositories.

Manufactured by H. A. Metz Laboratories, Inc., New York N. U. S. patent or trademark.

Paranitrobenzoic acid is obtained by the oxidation of paranitrotoluene, and this may be ethylated by the action of sulphuric acid and alcohol and the ester so obtained reduced to paraminobenzoic acid ethyl ester by the action of zinc and hydrochloric acid, or the acid may first be reduced and subsequently converted into the ethyl ester.

It is a white, crystalline powder, easily rendered impalpable, melting at from 90 to 91 C.; odorless and tasteless, but producing a sensation of numbness when placed on the tongue; almost insoluble in cold and with difficulty soluble in hot water; soluble in 6 parts of alcohol, in ether, benzene and to the amount of 2 to 3 per cent. in fatty oils. In oil solutions it may be sterilized without decomposition, but by prolonged boiling or by warming with dilute alkalis it is split up into alcohol and paraminobenzoic acid.

It should form clear, colorless and neutral solutions in alcohol or ether; after acidification with nitric acid it should not give a precipitate with silver nitrate. Its solution in dilute hydrochloric acid (1 to 10) is not affected by hydrogen sulphide. If a few drops of sodium nitrate solution be added to the slightly acidulated aqueous

solution followed by some alkaline betanaphthol solution, a cherry red coloration of bluish shade is produced, which changes to orange on further addition of hydrochloric acid. It is decomposed by prolonged heating with water and is incompatible with alkalies and their carbonates.

**BETA-EUCAINE HYDROCHLORIDE.**—For description see U. S. Pharmacopeia under Beta-Eucainæ Hydrochloridum.

*Actions and Uses.*—Beta-eucaine hydrochloride is a local anesthetic like cocaine, but weaker and devoid of the stimulating properties of the latter. It does not dilate the pupil, nor does it contract the blood-vessels as does cocaine. It has the advantage of stability even on prolonged boiling. It may be used in all cases in which cocaine is indicated as a local anesthetic, especially in ophthalmology.

*Dosage.*—It may be applied in a 2 or 3 per cent. solution to the eye, 5 to 10 per cent. for nose and throat and 5 to 10 per cent. for ointment for hemorrhoids.

**HOLOCAINE HYDROCHLORIDE.**—*Holocainæ Hydrochloridum.*—Ethenyl-Paradiethoxy-Diphenyl-Amidine Hydrochloride. —  $\text{CH}_2\text{C}(\text{NC}_6\text{H}_4\text{OC}_2\text{H}_5)(\text{NH.C}_6\text{H}_4\text{OC}_2\text{H}_5).\text{HCl}$ . — The hydrochloride of phenetidyl-acetphenetidin, a basic condensation product of paraphenetidin (para-ethoxy-amino-benzene) and acetparaphenetidin (phenacetin).

*Actions and Uses.*—Holocaine hydrochloride is a local anesthetic like cocaine, but having the advantage of a quicker effect and an antiseptic action. Five minims of a 1 per cent. solution when instilled into the eye are usually sufficient to cause anesthesia in from one to ten minutes. It is said not to cause the scaliness of the cornea which sometimes results after the use of the older remedy.

*Dosage.*—It is applied in a 1 per cent. aqueous solution prepared in porcelain vessels.

Manufactured by H. A. Metz Laboratories, Inc., New York. No U. S. patent.

Holocaine hydrochloride is prepared by the interaction of molecular proportions of paraphenetidin sulphate and acetphenetidin (phenacetin) in the presence of phosphorus oxychloride, decomposing the resulting holocaine sulphate with sodium hydroxide, crystallizing the base from alcohol, neutralizing it with hydrochloric acid, and crystallizing.

It forms small, colorless crystals, neutral or faintly alkaline, melting at 189 C., odorless, faintly bitter and producing transient numbness on the tongue. It is soluble in 50 parts of water and freely soluble in alcohol. On boiling in glass vessels the aqueous solution becomes turbid, owing to a separation of a small quantity of the free base by alkali derived from the glass.

Holocaine hydrochloride should form a clear, colorless solution in water, neutral or faintly alkaline, yielding a white precipitate on addition of silver nitrate or of ammonia. The base obtained by precipita-

tion with ammonia and crystallized from alcohol forms colorless needles which melt at 121 C. Incinerated on platinum, it leaves no weighable residue.

It is incompatible with alkalies and their carbonates and the usual alkaloidal reagents. Glass vessels should be avoided in preparing the solution, porcelain being used instead.

**PROCAINE.**— $\text{CH}_2(\text{C}_6\text{H}_4.(\text{NH}_2.\text{COO}).\text{CH}_2[\text{N}(\text{C}_2\text{H}_5)_2].\text{HCl}$ .  
—The monohydrochloride of para-amino-benzoyldiethyl-amino-ethanol. Procaine was introduced under the name novocaine.

*Actions and Uses.*—Procaine is a local anesthetic similar in action to cocaine, but less toxic than cocaine and other cocaine substitutes. When injected subcutaneously it exerts a prompt and powerful anesthetic action, but the effect is not sustained. This may be remedied by the simultaneous injection of epinephrine. Procaine is not irritant. (See note under Creosote and Guaiacol Compounds).

It is relatively ineffective when applied to intact mucous membranes.

*Dosage.*—For infiltration anesthesia, solutions of 0.25 Gm. (4 grains) procaine in 100 or 50 Cc. (3.2 or 1.6 ounces) physiologic sodium chloride solution, with 0.3 or 0.6 Cc. (5 or 10 minims) of epinephrine solution (1:1000); for installations and injections, solutions of 0.1 Gm. ( $1\frac{1}{2}$  grains) procaine in 10 or 5 Cc. (160 or 80 minims) physiologic sodium chloride solution, with or without 0.6 Cc. (10 minims) of epinephrine solution (1:1000). In ophthalmology, 1 to 5 to 10 per cent. solution, in rhinolaryngology, 5 to 20 per cent. solutions are recommended, with the addition of 0.4 to 0.5 Cc. (6 to 8 minims) of epinephrine solution (1:1000) to each 10 Cc. (160 minims). Internally, owing to its feeble toxicity, it may be given in doses up to 0.5 Gm. (8 grains) to adults.

Procaine is a colorless, odorless, crystalline substance, which, when placed on the tongue, produces a sense of numbness.

It melts at 153 to 155 C.

One Gm. of procaine is soluble in 0.7 Cc. of water and in 20 Cc. of alcohol, U. S. P., at 20 C. From the aqueous solution, which is neutral, alkali hydroxides and carbonates precipitate the free base in the form of a colorless oil, which soon congeals to a crystalline mass, but solution of sodium bicarbonate is miscible with solutions of procaine without producing precipitation or turbidity.

Dissolve 1 Gm. of procaine in 10 Cc. of water. Separate portions of the solution yield a white precipitate with potassium mercuric iodide test solution, a white precipitate with mercuric chloride test solution, a brown precipitate with iodine test solution, and a yellow precipitate with picric acid test solution. Acidify a portion with dilute nitric acid. A white curdy precipitate is formed on the addition of silver nitrate test solution.

Dissolve about 0.1 Gm. of procaine in 5 Cc. of water, add 2 drops of dilute hydrochloric acid and 2 drops of sodium nitrite solution (10 per cent.) and mix with a solution of 0.2 Gm. of betanaphthol in 10 Cc. of sodium hydroxide solution (10 per cent.). A scarlet red precipitate is formed.

To a solution of about 0.1 Gm. of procaine in 5 Cc. of water, add 3 drops of dilute sulphuric acid and mix with 5 drops of potassium permanganate test solution. The violet color of the latter disappears immediately (*distinction from cocaine*).



Dissolve about 0.1 Gm. of procaine in 1 Cc. of sulphuric acid, U. S. P. The solution is colorless (*organic impurities*).

Dissolve 0.1 Gm. of the salt in 10 Cc. of water and saturate with hydrogen sulphide. No coloration or precipitation occurs (*salts of heavy metals*).

Incinerate about 0.5 Gm. of procaine, accurately weighed. Not more than 0.1 per cent. of residue remains.

**Novocaine.**—A brand of procaine complying with the N. N. R. standards.

Manufactured by H. A. Metz Laboratories, Inc., New York, under U. S. patent No. 812,554 (Feb. 13, 1906; expires 1923) by license of the U. S. Federal Trade Commission. U. S. trademark No. 53,072.

*Novocaine Hypodermic Tablets "D."*—Each tablet contains novocaine 0.2 Gm. (3 grains).

*Novocaine Hypodermic Tablets "F."*—Each tablet contains novocaine 0.05 Gm. ( $\frac{5}{8}$  grain).

*Novocaine and L-Suprarenin Synthetic Hypodermic Tablets "A."*—Each tablet contains novocaine, 0.125 Gm. (2 grains) and l-suprarenin synthetic 0.000125 Gm. ( $\frac{1}{800}$  grain).

*Novocaine and L-Suprarenin Synthetic Hypodermic Tablets "B."*—Each tablet contains novocaine 0.1 Gm. ( $1\frac{1}{2}$  grains) and l-suprarenin synthetic 0.00025 Gm. ( $\frac{1}{250}$  grain).

*Novocaine and L-Suprarenin Synthetic Hypodermic Tablets "C."*—Each tablet contains novocaine 0.05 Gm. ( $\frac{5}{8}$  grain) and l-suprarenin synthetic 0.000083 Gm. ( $\frac{1}{800}$  grain).

*Novocaine and L-Suprarenin Synthetic Hypodermic Tablets "E."*—Each tablet contains novocaine 0.02 Gm. ( $\frac{1}{5}$  grain) and l-suprarenin synthetic 0.00005 Gm. ( $\frac{1}{2000}$  grain).

*Hypodermic Tablets Novocaine "T."*—Each tablet contains novocaine 0.02 Gm. ( $\frac{1}{5}$  grain) and l-suprarenin synthetic 0.00002 Gm. ( $\frac{1}{5000}$  grain).

**Procaine-Abbott.**—A brand of procaine complying with the N. N. R. standards.

Manufactured by the Abbott Laboratories, Chicago, under U. S. patent No. 812,554 (Feb. 13, 1906; expires 1923) by license of the U. S. Federal Trade Commission.

U. S. patent No. 1,260,289 (March 26, 1918; expires 1935).

**Procaine-Rector.**—A brand of procaine complying with the N. N. R. standards.

Manufactured by the Rector Chemical Company, Inc., New York, under U. S. patent No. 812,554 (Feb. 13, 1906; expires 1923) by license of the U. S. Federal Trade Commission.

**PROCAINE NITRATE.**— $\text{C}_6\text{H}_4\text{.NH}_2[\text{COO.C}_2\text{H}_4\text{.N(C}_2\text{H}_5)_2]\text{.HNO}_3$ .—The nitrate of l-para-aminobenzoyl-2-diethylaminoethane, the base contained in procaine.

*Actions and Uses.*—The same as those of procaine. It may be prescribed in combination with silver salts, with which it forms no precipitate.

*Dosage.*—Used in 3 per cent. solutions.

Procaine nitrate occurs in small colorless and odorless crystals, soluble in water and alcohol. The aqueous solution is neutral in reaction. Melting-point 100 to 102 C.

If 0.1 Gm. procaine nitrate be dissolved in 1 Cc. concentrated sulphuric acid and a solution of ferrous sulphate carefully floated above it, a brown zone is formed at the surface of contact of the two solutions. One part procaine nitrate dissolved in 10 parts water and acidified with nitric acid should yield no precipitate on the addition of silver nitrate solution.

**PROPAESIN.**—Propylis Aminobenzoas.—Propyl Amino-benzoate.—Paraminobenzoic Acid Propyl Ester.— $C_6H_4.NH_2.COO(C_3H_7)$ .—The propyl ester of 4-aminobenzoic acid,  $C_6H_4.NH_2.COOH$ .

*Actions and Uses.*—Propaesin is a local anesthetic and analgesic, similar in its action to anesthesin, ethyl aminobenzoate and cycloform, isobutyl aminobenzoate, said to be stronger than anesthesin. It is astringent and is said to be practically non-toxic. Externally it is said to be useful to reduce the sensibility of the mucous membranes of the nose, ear, and larynx, and to produce local anesthesia. It is also said to be of use in wounds and ulcers of the skin. Internally, it is claimed to be of value in all painful wounds and ulcers and other diseases of the mucous membranes, especially of the gastro-intestinal tract, including gastric ulcer and gastralgia. It is said to be useful for relieving pain in dental operations.

*Dosage.*—From 0.25 to 0.5 Gm. (4 to 8 grains) per dose, from 2 to 3 Gm. (30 to 45 grains) per day alone or mixed with sugar or other medicament or vehicle.

Externally it may be used in ointments of from 1 to 20 per cent.

Manufactured by Franz Fritzsche & Co., Hamburg, Germany (Par-mele Pharmacal Co., New York). U. S. patent No. 950,936 (March 1, 1910; expires 1927). U. S. trademark No. 74,856.

Propaesin is prepared by esterification of paraminobenzoic acid with propyl alcohol.

Propaesin is a fine, white or colorless, odorless, nearly tasteless powder, which produces numbness when placed on the tongue. Propaesin is very slightly soluble in water and is not readily wetted by this solvent. It is soluble in alcohol, benzine, chloroform and ether. Propaesin melts at 73 C.

When heated on platinum foil propaesin burns without leaving any ash; when heated with an excess of potassium hydroxide test solution it melts before boiling, forming an oily layer. By boiling this mixture the melted propaesin is saponified with the formation of propyl alcohol, which may be recognized by its odor. A clear, nearly colorless solution results, which, when neutralized with hydrochloric acid and cooled, gives a white precipitate of paraminobenzoic acid; the addition of a small quantity of ferric chloride test solution to the acidified solution gives a reddish brown color.

**STOVAIN.** — Benzoyl-Dimethylaminomethylpropanol Hydrochloride. —  $CH_3.CH_2.C(C_6H_5COO)(CH_3)CH_2N(CH_3)_2.HCl$ .—The hydrochloride of 2-benzyloxy-2-methyl-1-dimethyl-amino butane. It is closely related to alypin (which see).

*Actions and Uses.*—Stovaine acts as a local anesthetic. It has about the same power as cocaine, but dilates the blood-vessels, whereas cocaine contracts them. It is only one-third to one-half as toxic as cocaine.

It is used as a local anesthetic; while most reports are favorable, one case of gangrene has been reported following the use of a 10 per cent. solution.

*Dosage.*—Internally, 0.002 Gm. (1/30 grain) pill form. Locally it may be used in the eye in 4 per cent. solution and applied to other mucous membranes, as in laryngology, in from 5 to 10 per cent. solution. For hypodermic injections for local anesthesia it can be used in 0.75 to 1 per cent. solution.

Manufactured by the Poulenc Frères Co., Paris, France (Parmele Pharmacal Co., New York). U. S. patent Nos. 829,262, 829,374 (Aug. 21, 1906; expires 1923); 828,846 (Aug. 14, 1906; expires 1923). U. S. trademark No. 59,228.

Stovaine is prepared by causing a reaction of benzoyl chloride on the *α*-dimethyl-amino-pentonal-*β*, which is itself the product of reaction of ethylmagnesium chloride on methylaminoacetone.

It crystallizes in small, brilliant scales, which melt at 175 C. It is extremely soluble in water and easily in methyl alcohol and acetic ether, but requires 5 parts of absolute alcohol for solution and is only slightly soluble in acetone. It is quite stable and its solutions may be sterilized at 115 C. without suffering decomposition.

The aqueous solution is slightly acid to litmus, neutral to methyl orange. It is precipitated by all the alkaloidal reagents and is decomposed even by very dilute alkalis.

It is incompatible with alkalis and all alkaloidal reagents.

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**ARBUTIN.**—Arbutinum.— $C_{12}H_{16}O_7 + \frac{1}{2}H_2O$ .—A glucosid occurring in the leaves of *Arctostaphylos uva-ursi* Spr., *Vaccinium vitis-idaea* L. and many other genera of the family *ericaceae*.

*Actions and Uses.*—Arbutin probably owes its effect, at least in part, to the antiseptic action of hydroquinone, formed by its decomposition in the urinary tract. It has been used as a urinary antiseptic and diuretic.

*Dosage.*—From 0.2 to 0.5 Gm. (3 to 8 grains) three or four times a day.

Arbutin occurs in long, glistening, colorless needles, or as a fine, white, crystalline, odorless powder having a bitter taste. It is soluble in 8 parts of water and 16 parts of alcohol; very soluble in hot water and hot alcohol; insoluble in chloroform, ether and carbon disulphide. Its aqueous solution is neutral to litmus paper and is not precipitated by solutions of the metallic salts or by solution of tannin. Its aqueous solution is colored blue by ferric chloride test solution. By boiling with diluted sulphuric acid or by treatment with emulsin, arbutin is converted into glucose and hydroquinone.

When heated to 100 C. arbutin loses its water of hydration. At 195 C. the anhydrous glucosid melts. It should leave no residue on ignition. An aqueous solution of arbutin (1:20) should not be affected by hydrogen sulphide (*lead*).

**Arbutin-Abbott.**—A nonproprietary brand complying with the standards for arbutin.

Manufactured by the Abbott Laboratories, Chicago.

**Arbutin-Merck.**—A nonproprietary brand complying with the standards for arbutin.

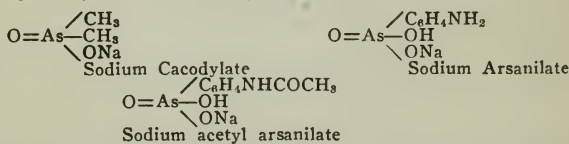
Merck & Co., New York, distributors.

## ARSENIC AND ARSENIC COMPOUNDS

In some of the compounds listed below, the arsenic is pentavalent; in others it is trivalent. A typical arsenic reaction results only from the trivalent arsenic, and in order to secure this action from those compounds containing pentavalent arsenic their arsenic must be reduced to the trivalent form; this is done by the body, but the rate at which the reduction occurs varies greatly with the different compounds. In some cases the desirable as well as the undesirable effects produced by these compounds are due to the arsenic which is slowly rendered active; in others the therapeutic effects may be due, at least in part, to the unaltered molecules. The diseases in which arsenic therapy has proved useful are particularly those caused by protozoa. Inorganic arsenic will kill protozoa, but it cannot be administered so as to reach the protozoa in fatal quantity. In the body, the organic compounds are less toxic to mammals and more toxic to protozoan parasites. In this way they become available for combating trypanosomes, syphilis, spirillosis and other protozoan infections.

Among the advantages claimed for or known to be possessed by these compounds the following may be mentioned: In those known to produce their effects through the liberation of arsenic, the arsenic is liberated slowly; some remain in the circulating blood for a much longer period than do inorganic arsenic compounds and thus remain longer in contact with parasites which it is desired to kill; some are specifically etiotropic, that is, they have a much greater affinity for the parasites causing the disease than they have for the tissues of the host.

### COMPOUNDS CONTAINING PENTAVALENT ARSENIC



Arsanilic acid is derived from arsenic acid,  $\text{As}_2\text{O}_5 \cdot (\text{OH})_3$ , by replacing one hydroxyl by aniline (phenylamine)  $\text{C}_6\text{H}_5\text{NH}_2$ ; related compounds are made by substituting derivatives of aniline.



The compounds containing pentavalent arsenic are comparatively non-toxic when introduced into the animal system until changes take place that liberate the arsenic. When they are slowly decomposed they produce favorable effects. If the reduction takes place with greater rapidity they may produce ordinary arsenic poisoning.

Sodium cacodylate is excreted partly unchanged and partly as cacodylic oxide, which gives a foul odor to the breath, perspiration, etc. Further changes yield products containing inorganic, trivalent arsenic by which the therapeutic effects are produced.

Sodium arsanilate has been used chiefly against trypanosomes. It has no direct action on these parasites, but owes its effects to the products of its reduction in the system. These products appear to be organic compounds containing the arsenic in the trivalent form. Artificial reduction products, which vary according to conditions, are much more active than the arsanilate, and paraminophenyl arsenous acid kills the parasites in the test-tube. B. T. Terry has found that emulsions of liver and blood reduce arsanilate into directly effective products.

In poisonous doses or when excessive reduction occurs, sodium arsanilate may produce the ordinary toxic effects of arsenic, but acts with especial violence on the optic nerve, producing permanent blindness from optic atrophy. This result may unfortunately occur with therapeutic doses.

#### COMPOUNDS CONTAINING TRIVALENT ARSENIC

According to Ehrlich's view only trivalent arsenic is markedly toxic to spirochetes, trypanosomes, etc.; hence he introduced a number of such compounds. Of these only the arsphenamines, in which the toxicity is reduced or modified by the introduction into the molecules of certain groups, are listed below. These compounds have, according to Ehrlich, a special affinity to certain organisms, particularly spirochetes, while their toxicity for the higher animals is comparatively low. The exact fields of usefulness of these compounds and their limitations, and also the best methods of administering them, are still under discussion.

The arsphenamines have a direct action on the protozoa and also on some bacteria (anthrax). This activity is enhanced by the presence of enzymes from the liver and especially from the blood.

The toxic actions of arsphenamine are ascribed to the arsenic component in some cases. In other cases the decomposition of the solution has been assigned as a cause. The presence of bacteria in the distilled water is believed to cause the febrile phenomena. The so-called "nervous relapses" are explained as due to a renewal of vigor in the few spirochetes which remain after the arsphenamine has destroyed most of those present in the system at the time when the drug was administered.



The ratio between etiotropic efficiency and toxicity is far more favorable in arspenamine than in any of the other organic arsenic compounds thus far tested. Arsenic has been found in the parts infected with syphilis while absent from other localities, indicating that the efficient arsenical compounds combine with the spirochetes or their products in the tissues.

Arsphenamines are contraindicated or should be used with special caution in diseases of the eye of a non-syphilitic character; in severe affections of the heart and blood-vessels, the lungs and kidneys; and in advanced degenerative processes in the central nervous system. They should also be used with caution in infants.

### Arsenic Compounds, Complex—Arsanilates

Arsanilic acid is derived from arsenic acid,  $\text{AsO}(\text{OH})_2$ , by replacing one hydroxyl by aniline (phenylamine); related compounds are made by substituting derivatives of aniline.

**SODIUM ARSANILATE.**—Sodii Arsanilas.—Sodium Aniline Arsonate.—Sodium Aminophenyl Arsonate.— $\text{C}_6\text{H}_4(\text{NH}_2)(\text{AsO}(\text{OH})\text{ONa})$ .—The sodium salt of arsanilic acid,  $\text{C}_6\text{H}_4(\text{NH}_2)(\text{AsO}(\text{OH})_2)$ , 1:4.

*Actions and Uses.*—The arsenic of the arsanilic acid is liberated very slowly in the system, thus producing the ordinary therapeutic effects of arsenic, with a more continuous and less toxic action and less irritation. Toxic effects from excessive doses have been frequently noted, although the toxicity of sodium arsanilate is stated to be about one-fortieth of that of arsenic trioxide. The poisonous effects appear to be due largely to the arsenic component, the aniline taking no part in them. It is claimed that the use of sodium arsanilate is not followed by irritation, abscess formation, etc., which sometimes follow the use of other preparations of arsenic. The use of sodium arsanilate in large doses has occasionally been followed by degeneration of the optic nerve, leading to blindness.

Sodium arsanilate has been recommended for the conditions which are favorably influenced by arsenic, such as anemia, nervous conditions and diseases of the skin. It is said to have been very successful as a remedy for trypanosomiasis, both of animals and of man, and is also said to be useful in other protozoal diseases, such as syphilis, malaria and kala-azar.

*Dosage.*—From 0.02 to 0.2 Gm. ( $\frac{1}{3}$  to 3 grains) hypodermically every other day, gradually increasing, if necessary, until the single dose reaches 0.65 Gm. (10 grains) and until a total of 6.5 Gm. (100 grains) have been given. The drug should not be given by the mouth, as it is decomposed by the acid contents of the stomach, and toxic symptoms may result.

Arsanilic acid is prepared by condensing aniline and arsenic acid, eliminating water and isolating the reaction product. The sodium salt is prepared by the usual methods.

Sodium arsanilate occurs as white, odorless crystals soluble in (5 or 6 parts) water and is more soluble in warm water. It has a faint salty taste. On standing the aqueous solution assumes a yellowish tint. Sodium arsanilate crystallizes with somewhat varying amounts of water of crystallization. The arsenic content varies in different preparations from 23 to 26 per cent.

An acid solution of sodium arsanilate is not affected by hydrogen sulphide in the cold; when the solution is warmed the arsenic may be completely precipitated by hydrogen sulphide. If a solution of sodium arsanilate is treated with hydrochloric acid and potassium iodide, iodine is set free. The resulting liquid, whether freed of iodine or not, gives, even in the cold, a precipitate of arsenic sulphide when treated with hydrogen sulphide. The arsenic and water content of sodium arsanilate may be determined by the methods given in *THE JOURNAL A. M. A.*, Sept. 21, 1907, p. 1041. (Reports of the Chemical Laboratory of the American Medical Association, 1908, p. 13). An aqueous solution of the salt gives with mineral acids a white precipitate of arsanilic acid, soluble in excess of acid. An aqueous solution of the salt gives with silver nitrate solution a white precipitate of silver arsanilate. An aqueous solution of the salt, after the addition of hydrochloric acid and sodium nitrite gives a deep-red coloration with a solution of betanaphthol in caustic soda.

## Arsenic Compounds, Complex—Arsenphenolamines

### ARSPHENAMINE AND NEOARSPHENAMINE

**ARSPHENAMINE.**—Arsenphenolamine Hydrochloride.—Arsenphenolaminae Hydrochloricum.— $\text{HCl} \cdot \text{NH}_2 \cdot \text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{As}$ :  $\text{As} \cdot \text{C}_6\text{H}_4 \cdot \text{OH} \cdot \text{NH}_2 \cdot \text{HCl} + 2\text{H}_2\text{O}$ .—The hydrochloride of 3-diamino-4-dihydroxy-1-arsenobenzene, corresponding to 31.57 per cent. arsenic (As).

*Actions and Uses.*—Arsphenamine is useful as a specific remedy for syphilis in all stages. It is asserted that this drug gives especially favorable results in those cases which prove rebellious to mercury and iodids. According to available data, in incipient tabes, early paralysis, and epilepsy due to syphilis, the remedy can be employed with the prospect of cure only in those cases in which its use is begun immediately after the first symptoms of the secondary disease have appeared.

It is stated that the remedy is useful in all spirillum affections, such as relapsing fever, frambesia, and in malaria; it is also said to be an available substitute for arsenic in the treatment of diseases of the skin, nerves and blood.

The remedy is contraindicated in severe disturbances of the circulatory organs, advanced degenerations of the central nervous system, fetid bronchitis, and cachexias, unless these are a direct result of syphilis; it is also contraindicated in patients who have pronounced idiosyncrasy against arsenic.

It has been employed successfully in various types of syphilitic disease of the eyes. Repeated injections should be given.

*Dosage.*—From 0.3 to 0.6 Gm. (5 to 9 grains).

For children from 0.2 to 0.3 Gm. (3 to 5 grains). In infants doses of from 0.02 to 0.1 Gm. ( $\frac{1}{3}$  to  $1\frac{1}{2}$  grains) may be used. The dose should be varied according to the strength and condition of the patient. The intravenous method is, on the whole, preferable and is especially to be recommended.

For intravenous injection proceed as follows:

The ampule containing the drug is wiped off with alcohol, the neck filed across and broken off, and the contents emptied into a sterile glass-stoppered mixing cylinder containing, preferably, a number of small glass beads. Sterile distilled water is added, and with shaking the drug passes into solution. A 15 per cent. solution of caustic soda is now added, drop by drop, to the solution in the cylinder. A precipitate of the base is first deposited, and on further addition of caustic soda, aided by shaking, this is again brought into solution, the fluid being strongly alkaline. The amount of alkali necessary is about 4 drops of a 15 per cent. solution for each 0.1 Gm. of arsphenamine; thus, for 0.6 Gm., 1.14 Cc., or about from 23 to 45 drops of 15 per cent. solution of caustic soda, would be required.

Dilute with sterile distilled water to make 30 Cc. for each 0.1 Gm. of the drug.

At least fifteen minutes should be allowed for the solution to flow into the vein.

The directions accompanying the drug as to temperature of water, etc., should be followed.

Syphilographers have practically discarded the intramuscular injections as well as the subcutaneous.

In all cases the skin should be disinfected with tincture of iodine.

In the treatment of syphilis of the central nervous system the Swift-Ellis method of intraspinal treatment is utilized at times. The technic is as follows:

An injection of the usual dose of arsphenamine or neoarsphenamine is given intravenously. One hour after the injection 40 Cc. of blood are withdrawn by venipuncture. This is allowed to clot and left on ice for twenty-four hours. The serum is then pipetted off and centrifuged; 12 Cc. of this serum is usually added to 18 Cc. of sterile normal salt solution to make a 40 per cent. solution of salvarsanized serum although it may be used without dilution. This is then heated for thirty minutes at 56 C. Before making the intraspinal injection a volume of spinal fluid equal to that of the injection is often withdrawn.

In tabes dorsalis the results of this method are, as a rule, highly satisfactory—more so than with the ordinary intravenous therapy. The pains have disappeared, the reaction in the cerebrospinal fluid has returned more or less completely to normal, and certain symptoms, such as diminution of bladder control and sexual power, which are usually

looked on as fundamental phenomena, may disappear entirely or be greatly improved. Patients also feel better.

In cerebrospinal syphilis also the intraspinal method has been used to a considerable extent. It is questionable, however, whether the results are much better than those of the intravenous method.

In dementia paralytica the results of this method have been outspokenly disappointing.

The contents of a tube should be used at once after opening and under no circumstances should the contents of a tube damaged in transportation or any remnants of the powder from previously opened tubes be used.

Arsphenamine is prepared by the nitration of p-oxy-phenyl-arsinic acid and subsequent reduction and condensation of the resulting nitro-phenyl-arsinic acid.

Arsphenamine is a yellow, crystalline, hygroscopic powder, very unstable in air. It is readily soluble in water, yielding a solution with an acid reaction. The addition of sodium hydroxide solution to an aqueous solution of arsphenamine, in the ratio of two molecules of sodium hydroxide to one of arsphenamine, precipitates the free base ( $\text{NH}_2\text{OH}\cdot\text{C}_6\text{H}_3\text{As}:\text{As}\cdot\text{C}_6\text{H}_3\text{OH}\cdot\text{NH}_2$ ). On the addition of an aqueous solution of sodium carbonate to an aqueous solution of arsphenamine, a precipitate is produced which is insoluble in an excess of the reagent.

An aqueous solution of arsphenamine is not affected by the addition of dilute hydrochloric, nitric or sulphuric acids. When arsphenamine is heated with an alkaline solution of potassium permanganate the permanganate solution is reduced and ammonia given off. The addition of ferric chloride solution to an aqueous solution of arsphenamine produces a brownish-violet color, which gradually changes to a dark red; finally the liquid becomes turbid. Silver nitrate solution added to an aqueous solution of arsphenamine acidified with dilute nitric acid yields a dark yellow precipitate which rapidly becomes black. The addition of concentrated nitric acid to an aqueous solution of arsphenamine produces a yellowish-white precipitate. On further addition of the acid the precipitate redissolves and the solution becomes dark red. The arsenic content of arsphenamine may be estimated according to the method described in Public Health Reports, 33:1003 (June 21) 1918. The total arsenic content of the air-dried drug shall not be below 29.5 or above 31.50 per cent.

To determine the toxicity of arsphenamine select not less than four healthy albino rats, weighing between 100 and 150 grams (pregnant animals shall not be used). Prepare a slightly alkaline 2 per cent. solution of the drug, using freshly distilled water, and inject the solution into the saphenous or tail vein of each rat at the rate of not more than 0.5 Cc. per minute. The rats shall *not* be anesthetized for the injection. At least 75 per cent. of the series of animals, injected with the maximum tolerated dose, should survive forty-eight hours from the time of injection; the maximum tolerated dose shall not be below 80 mg. per kilo body weight.

Arsphenamine may be marketed only in colorless glass ampules containing an atmosphere of an inert gas or in a vacuum.

#### Arsaminol.—A brand of arsphenamine.

Manufactured by the Takamine Laboratory, Inc., New York, under U. S. patents Nos. 986,148 (March 7, 1911; expires 1928), 1,081,897 (Dec. 16, 1913; expires 1930), 1,081,592 (Dec. 16, 1913; expires 1930),



and 1,116,398 (Nov. 10, 1914; expires 1931) by license of the U. S. Federal Trade Commission.

*Arsaminol 0.1 Gm. Tubes.*—Each hermetically sealed tube contains arsaminol 0.1 Gm.

*Arsaminol 0.2 Gm. Tubes.*—Each hermetically sealed tube contains arsaminol 0.2 Gm.

*Arsaminol 0.3 Gm. Tubes.*—Each hermetically sealed tube contains arsaminol 0.3 Gm.

*Arsaminol 0.4 Gm. Tubes.*—Each hermetically sealed tube contains arsaminol 0.4 Gm.

*Arsaminol 0.5 Gm. Tubes.*—Each hermetically sealed tube contains arsaminol 0.5 Gm.

*Arsaminol 0.6 Gm. Tubes.*—Each hermetically sealed tube contains arsaminol 0.6 Gm.

**Arsenobenzol (Dermatological Research Laboratories).**—A brand of arsphenamine.

Manufactured by the Dermatological Research Laboratories, Philadelphia, Pa., under U. S. patent Nos. 986,148 (March 7, 1911; expires 1928), 1,081,897 (Dec. 16, 1913; expires 1930), 1,081,592 (Dec. 16, 1913; expires 1930), and 1,116,398 (Nov. 10, 1914; expires 1931) by license of the U. S. Federal Trade Commission.

*Arsenobenzol (Dermatological Research Laboratories) 0.4 Gm. Ampules.*—Each hermetically sealed ampule contains arsenobenzol (Dermatological Research Laboratories) 0.4 Gm.

*Arsenobenzol (Dermatological Research Laboratories) 0.6 Gm. Ampules.*—Each hermetically sealed ampule contains arsenobenzol (Dermatological Research Laboratories) 0.6 Gm.

*Arsenobenzol (Dermatological Research Laboratories) 1 Gm. Ampules.*—Each hermetically sealed ampule contains arsenobenzol (Dermatological Research Laboratories) 1 Gm. Prepared for use in hospitals in divided doses.

**Diarsenol.**—A brand of arsphenamine.

Manufactured by the Synthetic Drug Co., Toronto, Canada (Diarsenol Company, Inc., Buffalo, New York) under U. S. patent Nos. 986,148 (March 7, 1911; expires 1928), 1,081,897 (Dec. 16, 1913; expires 1930), 1,081,592 (Dec. 16, 1913; expires 1930) and 1,116,398 (Nov. 10, 1914; expires 1931) by license of the U. S. Federal Trade Commission. Canadian patent No. 133,636. U. S. trademark Nos. 90,128 and 90,129.

*Diarsenol, 0.1 Gm. Ampoules.*—Each hermetically sealed ampule contains diarsenol 0.1 Gm.

*Diarsenol, 0.2 Gm. Ampoules.*—Each hermetically sealed ampule contains diarsenol 0.2 Gm.

*Diarsenol, 0.3 Gm. Ampoules.*—Each hermetically sealed ampule contains diarsenol 0.3 Gm.

*Diarsenol, 0.4 Gm. Ampoules.*—Each hermetically sealed ampule contains diarsenol 0.4 Gm.

*Diarsenol, 0.5 Gm. Ampoules.*—Each hermetically sealed ampule contains diarsenol 0.5 Gm.

*Diarsenol, 0.6 Gm. Ampoules.*—Each hermetically sealed ampule contains diarsenol 0.6 Gm.

*Diarsenol, 1.0 Gm. Ampoules.*—Each hermetically sealed ampule contains diarsenol 1.0 Gm.

*Diarsenol, 2.0 Gm. Ampoules.*—Each hermetically sealed ampule contains diarsenol 2.0 Gm.

*Diarsenol, 3.0 Gm. Ampoules.*—Each hermetically sealed ampule contains diarsenol 3.0 Gm.



**Salvarsan.**—A brand of arsphenamine.

Manufactured by H. A. Metz Laboratories, Inc., New York, under U. S. patent Nos. 986,148 (March 7, 1911; expires 1928), 1,081,897 (Dec. 16, 1913; expires 1930), 1,081,592 (Dec. 16, 1913; expires 1930) and 1,116,398 (Nov. 10, 1914; expires 1931) by license of the U. S. Federal Trade Commission. U. S. trademark No. 40,734.

*Salvarsan 0.1 Gm. Tubes.*—Each hermetically sealed tube contains salvarsan 0.1 Gm.

*Salvarsan 0.2 Gm. Tubes.*—Each hermetically sealed tube contains salvarsan 0.2 Gm.

*Salvarsan 0.3 Gm. Tubes.*—Each hermetically sealed tube contains salvarsan 0.3 Gm.

*Salvarsan 0.4 Gm. Tubes.*—Each hermetically sealed tube contains salvarsan 0.4 Gm.

*Salvarsan 0.5 Gm. Tubes.*—Each hermetically sealed tube contains salvarsan 0.5 Gm.

*Salvarsan 0.6 Gm. Tubes.*—Each hermetically sealed tube contains salvarsan 0.6 Gm. (9 grains).

*Salvarsan 1 Gm. Tube.*—Each hermetically sealed tube contains salvarsan 1 Gm.

*Salvarsan 2 Gm. Tubes.*—Each hermetically sealed tube contains salvarsan 2 Gm.

*Salvarsan 3 Gm. Tubes.*—Each hermetically sealed tube contains salvarsan 3 Gm.

**NEOARSPHENAMINE.**—**Arsenphenolamine-S.**—A mixture of sodium 3-diamino-4-dihydroxy-1-arsenobenzene-sulphoxylate,  $\text{NH}_2.\text{OH}.\text{C}_6\text{H}_3.\text{As}:\text{As}.\text{C}_6\text{H}_3.\text{OH}.\text{NH}.\text{(CH}_2\text{O)OSNa}$ , with inert inorganic salts. The arsenic content of 3 parts of neoarsphenamine is approximately equal to that of 2 parts of arsphenamine.

*Actions and Uses.*—Since neoarsphenamine is merely a soluble compound of arsphenamine, its actions and uses are the same as those of arsphenamine, which see. Preference should always be given to arsphenamine when it is practicable to administer it.

*Dosage.*—Neoarsphenamine is said to be tolerated better than arsphenamine, and consequently may be employed in larger doses. The average dose for men is 0.75 Gm. (11.6 grains) with 0.6 Gm. (9.3 grains) and 0.9 Gm. (13.9 grains) as the minimum and maximum doses. For women 0.6 Gm. (9.3 grains) is the average, 0.45 Gm. (6.9 grains) and 0.75 Gm. (11.6 grains) as minimum and maximum. Children may be given from 0.15 Gm. (2.3 grains) to 0.3 Gm. (4.6 grains).

Neoarsphenamine may be administered by intravenous or intramuscular injection, the former being considered decidedly preferable, but owing to the danger of infiltrations, it must not be administered subcutaneously. For intravenous injections 25 Cc. of freshly distilled water should be used for each 0.15 Gm. of neoarsphenamine. For the intramuscular injections 3 Cc. (45 minims) of freshly distilled water should be used for each 0.15 Gm. (2.3 grains) of neoarsphenamine this yielding an approximately isotonic solution.

Neoarsphenamine may be employed intravenously in concentrated solutions. For this purpose 0.45 to 0.6 Gm. is dissolved in 10 Cc. sterile freshly distilled water and 0.75 to 0.9 Gm. is dissolved in 15 Cc. and the injection made with a syringe instead of by gravity.

Solutions should be freshly prepared, from freshly distilled sterile cold water, or, if this is unavailable, with well boiled and cooled tap water.

Solutions of neoarsphenamine must be injected immediately after their preparation. Neoarsphenamine solution must not be warmed and the temperature of the injection fluid should not be more than 20 to 22 C. (68 to 71.6 F.).

Neoarsphenamine is prepared by precipitating a salt of 3-diamino-4 dihydroxy-1-arsenobenzene with sodium methanal-sulphoxylate and dissolving the precipitate in alkalis. From the resultant solution neoarsphenamine is obtained by the addition of alcohol or acetone, or by evaporation of the sodium in a vacuum.

Neoarsphenamine is an orange-yellow powder possessing a peculiar odor. It is very unstable in the air. Neoarsphenamine is readily soluble in water, yielding a yellow solution which is neutral toward litmus. Upon standing the aqueous solution becomes dark brown, forming a brown precipitate.

A freshly prepared aqueous solution of neoarsphenamine (1:100) yields a precipitate on the addition of mineral acids. If silver nitrate test solution be added to an aqueous solution of neoarsphenamine (1:100) a brownish color should be produced, quickly followed by the formation of a black precipitate. If ferric chloride test solution be added to an aqueous solution of neoarsphenamine (1:100) a violet color should be produced, which soon changes to a dark red. If to 10 Cc. of the aqueous solution of neoarsphenamine (1:100) 5 Cc. of diluted hydrochloric acid be added and the mixture heated, the irritating odor of sulphur dioxide will be evolved. If to 10 Cc. of the aqueous solution of neoarsphenamine (1:100) 5 Cc. of diluted hydrochloric acid be added, the precipitate collected on the filter and treated with zinc dust and warm, diluted hydrochloric acid in a test-tube, and if paper moistened with a 5 per cent. cadmium chloride solution be held in the mouth of the tube, the paper should be stained yellow within a few minutes (distinction from *arsphenamine*). If to 10 Cc. of the aqueous solution of neoarsphenamine (1:100) 5 Cc. of diluted hydrochloric acid be added, the precipitate removed by filtration, 2 Cc. of barium chloride test solution added to the filtrate, the mixture allowed to stand for twelve hours, the precipitate of barium sulphate removed by the filtration, 5 Cc. of nitric acid added to the filtrate, the mixture boiled and evaporated to dryness, the residue should not be completely soluble in 50 Cc. of hot water slightly acidified with hydrochloric acid. The arsenic content of neoarsphenamine may be estimated according to the method described in *Public Health Reports* 33:1003 (June 21) 1918.

The toxicity of neoarsphenamine should be such that rats survive 180 mg. per kilogram when a 4 per cent. solution is given intravenously.

**Neoarsphenamine (Dermatological Research Laboratories).**  
—A brand of neoarsphenamine.

Manufactured by the Dermatological Research Laboratories, Philadelphia, Pa., under U. S. patent reissue No. 13,848 (Dec. 15, 1914; expires 1931) by license of the U. S. Federal Trade Commission.

*Neoarsphenamine (Dermatological Research Laboratories) 0.1 Gm. Ampules.*—Each hermetically sealed ampule contains neoarsphenamine (Dermatological Research Laboratories) 0.1 Gm.

*Neoarsphenamine (Dermatological Research Laboratories) 0.3 Gm. Ampules.*—Each hermetically sealed ampule contains neoarsphenamine (Dermatological Research Laboratories) 0.3 Gm.

*Neoarsphenamine (Dermatological Research Laboratories) 0.45 Gm. Ampules.*—Each hermetically sealed ampule contains neoarsphenamine (Dermatological Research Laboratories) 0.45 Gm.

*Neoarsphenamine (Dermatological Research Laboratories) 0.6 Gm. Ampules.*—Each hermetically sealed ampule contains neoarsphenamine (Dermatological Research Laboratories) 0.6 Gm.

*Neoarsphenamine (Dermatological Research Laboratories) 0.75 Gm. Ampules.*—Each hermetically sealed ampule contains neoarsphenamine (Dermatological Research Laboratories) 0.75 Gm.

*Neoarsphenamine (Dermatological Research Laboratories) 0.9 Gm. Ampules.*—Each hermetically sealed ampule contains neoarsphenamine (Dermatological Research Laboratories) 0.9 Gm.

### Neodiarsenol.—A brand of neoarsphenamine.

Manufactured by the Synthetic Drug Company, Toronto, Canada (Darsenol Company, Inc., Buffalo, New York) under U. S. patent, reissue No. 13,848 (Dec. 15, 1914; expires 1931) by license of the U. S. Federal Trade Commission. Canadian patent No. 144,874. U. S. trademark Nos. 90,128 and 90,129.

*Neodiarsenol, 0.15 Gm. Ampoules.*—Each hermetically sealed ampule contains neodiarsenol, 0.15 Gm.

*Neodiarsenol, 0.3 Gm. Ampoules.*—Each hermetically sealed ampule contains neodiarsenol, 0.3 Gm.

*Neodiarsenol, 0.45 Gm. Ampoules.*—Each hermetically sealed ampule contains neodiarsenol, 0.45 Gm.

*Neodiarsenol, 0.6 Gm. Ampoules.*—Each hermetically sealed ampule contains neodiarsenol, 0.6 Gm.

*Neodiarsenol, 0.75 Gm. Ampoules.*—Each hermetically sealed ampule contains neodiarsenol, 0.75 Gm.

*Neodiarsenol, 0.9 Gm. Ampoules.*—Each hermetically sealed ampule contains neodiarsenol, 0.9 Gm.

### Neosalvarsan.—A brand of neoarsphenamine.

Manufactured by H. A. Metz Laboratories, Inc., New York, under U. S. patent reissue No. 13,848 (Dec. 15, 1914; expires 1931), by license of the U. S. Federal Trade Commission. U. S. trademark.

*Neosalvarsan, Dose I.*—Each sealed tube contains neosalvarsan, 0.15 Gm.

*Neosalvarsan, Dose II.*—Each sealed tube contains neosalvarsan, 0.3 Gm.

*Neosalvarsan, Dose III.*—Each sealed tube contains neosalvarsan, 0.45 Gm.

*Neosalvarsan, Dose IV.*—Each sealed tube contains neosalvarsan, 0.6 Gm.

*Neosalvarsan, Dose V.*—Each sealed tube contains neosalvarsan, 0.75 Gm.

*Neosalvarsan, Dose VI.*—Each sealed tube contains neosalvarsan, 0.9 Gm.

*Neosalvarsan, Dose X.*—Each sealed tube contains neosalvarsan, 1.5 Gm.

*Neosalvarsan, Dose XX.*—Each sealed tube contains neosalvarsan, 3.0 Gm.

*Neosalvarsan, Dose XXX.*—Each sealed tube contains neosalvarsan, 4.5 Gm.

**Arsenic Compounds, Complex—Organic—Cacodylates**

**CALCIUM CACODYLATE.**—*Calcii Cacodylas.*—A calcium salt of cacodylic acid containing from 43.5 to 48 per cent. of arsenic in the form of cacodylic acid and free from arsenite, arsenate and monomethylarsenate.

*Actions and Uses.*—Calcium cacodylate has the mild arsenic action of cacodylates. Its action is essentially the same as that of sodium cacodylate but it is preferred by some.

*Dosage.*—0.045 Gm. ( $\frac{3}{4}$  grain), repeated if necessary, at twenty-four hour intervals.

*Ampuls Calcium Cacodylate Solution—Mulford.*—Each ampule contains calcium cacodylate 0.045 Gm. ( $\frac{3}{4}$  grain) in 1 Cc. sterile physiological sodium chloride solution.

The calcium cacodylate used in the preparation of these ampules complies to the following tests:

No turbidity is produced in 10 Cc. of an aqueous solution of the salt (1:20) by 1 Cc. of calcium chloride test solution, either in the cold or upon heating (*monomethylarsenate*). No yellow precipitate is produced in an aqueous solution of the salt (1:20) by ammonium molybdate test solution; nor is a yellow precipitate produced by sodium thiosulphate test solution; nor is a yellow precipitate produced by hydrogen sulphide test solution. No white precipitate is produced in an aqueous solution of the salt, after acidulating with hydrochloric acid, by barium chloride test solution.

Dissolve 1 to 2 Gm. calcium cacodylate, accurately weighed, in 25 Cc. distilled water, then titrate with normal hydrochloric acid volumetric solution, using methyl orange as indicator. Each gram of calcium cacodylate requires not less than 4.3 Cc. nor more than 5.6 Cc. of normal acid; if to the finished titration phenolphthalein solution is added, 5.8 to 6.4 Cc. of normal volumetric potassium hydroxide is required to produce a red color for each gram of calcium cacodylate, showing not less than 43.5 per cent. nor more than 48.0 per cent. arsenic (As). Theoretically calcium cacodylate,  $\text{Ca}[(\text{CH}_3)_2\text{AsO}_2]_2$ , contains 47.7 per cent. arsenic.

Prepared by H. K. Mulford Company, Philadelphia.

Calcium cacodylate occurs as a white, granular powder, almost odorless or having a slight odor of hydrogen arsenide. It is very soluble in water.

Calcium cacodylate loses about 8.5 per cent. of its weight when dried at 100 C.

The aqueous solution of calcium cacodylate is alkaline to litmus, but acid to phenolphthalein.

With silver nitrate test solution an aqueous solution of the salt (1:20) yields a white precipitate, soluble in nitric acid or ammonia water.

A mixture of 1 Cc. of an aqueous solution (1:100) of the salt with 10 Cc. of hypophosphorous acid develops the disgusting odor of cacodyl (caution on account of the extreme poisonous nature of the gas).

**FERRIC CACODYLATE.**—*Ferri Cacodylas.*—Iron Cacodylate.—A ferric salt of cacodylic acid containing from 39.7 to 44.9 per cent. arsenic (As).

*Actions and Uses.*—Ferric cacodylate has the properties of iron salts and of arsenic. Its use has been proposed in conditions in which the effects of iron and the mild arsenic action of cacodylates is desired.



*Dosage.*—From 0.015 to 0.1 Gm. ( $\frac{1}{4}$  to  $1\frac{1}{2}$  grains).

*Ampuls Iron Cacodylate-Mulford, 0.03 Gm. ( $\frac{1}{2}$  gr.).*—Each ampule contains iron cacodylate, 0.03 Gm. ( $\frac{1}{2}$  grain), in 1 Cc.

Prepared by H. K. Mulford Company, Philadelphia.

*Ampoules Iron Cacodylate, Squibb, 0.03 Gm. ( $\frac{1}{2}$  gr.).*—Each ampule contains iron cacodylate, 0.03 Gm. ( $\frac{1}{2}$  grain), in 1 Cc.

Prepared by E. R. Squibb and Sons, New York City.

Ferric cacodylate occurs as a slight grayish-brown powder, having an apple-like odor. An aqueous solution of the salt is acid to litmus and to phenolphthalein. One part of ferric cacodylate is soluble in about 16 parts of cold water.

Ferric cacodylate loses about 5 per cent. of its weight when dried at 100 C.

With silver nitrate test solution, an aqueous solution of the salt (1:20) yields a white precipitate, soluble in nitric acid or ammonia water.

A mixture of 1 Cc. of an aqueous solution (1:100) of the salt with 10 Cc. of hypophosphorus acid develops the disgusting odor of cacodyl (caution on account of the extreme poisonous nature of the gas).

The ferric cacodylate used in the preparation of Ampuls Iron Cacodylate-Mulford, 0.03 Gm., complies to the following tests:

No turbidity is produced in 10 Cc. of an aqueous solution of the salt (1:20) by 1 Cc. of calcium chloride test solution, either in the cold or on heating (*monomethylarsenate*). No yellow precipitate is produced in an aqueous solution of the salt (1:20) by ammonium molybdate test solution; nor is a yellow precipitate produced by sodium thiosulphate test solution. A white turbidity, but no yellow precipitate, is produced in 10 Cc. of an aqueous solution of the salt (1:20), acidulated with hydrochloric acid, on addition of 10 Cc. of hydrogen sulphide test solution. A portion of an aqueous solution of the salt (1:20), acidulated with hydrochloric acid, is not rendered turbid at once by barium chloride test solution.

Dissolve about 1 Gm. of ferric cacodylate, accurately weighed, in 200 Cc. distilled water, then titrate with normal sodium hydroxide volumetric solution, using 5 Cc. of phenolphthalein test solution as indicator. Each gram of ferric cacodylate requires not less than 5.3 Cc. nor more than 5.6 Cc. of normal sodium hydroxide volumetric solution; showing not less than 39.7 per cent. nor more than 41.9 per cent. arsenic (As). Theoretically ferric cacodylate,  $\text{Fe}[(\text{CH}_3)_2\text{AsO}_2]_3$ , contains 48.1 per cent. arsenic.

The ferric cacodylate used in the preparation of Ampoules Iron Cacodylate, Squibb, 0.03 Gm., complies to the following tests:

An aqueous solution of ferric cacodylate (1:20) does not at once become blue on the addition of potassium ferricyanide test solution (*ferrous iron*).

A few drops of an aqueous solution of ferric cacodylate (1:100) mixed with 2 Cc. of hypophosphorus acid in a stoppered test tube develops the odor of cacodyl within one hour.

Five Cc. portions of an aqueous solution of ferric cacodylate (1:20) does not become turbid on the addition of silver nitrate test solution, lead acetate test solution or cobalt nitrate test solution (*monomethylarsenate*).

No turbidity is produced in 5 Cc. of an aqueous solution of ferric cacodylate (1:20) by 1 Cc. of calcium chloride test solution, either in the cold or on heating (*monomethylarsenate*).

An aqueous solution of ferric cacodylate (1:20), from which the iron has been removed by precipitation with ammonia water and filtering, acidulated with hydrochloric acid, yields on addition of an equal volume of hydrogen sulphide test solution not more than a slight coloration (*heavy metals and arsenites*).



**SODIUM CACODYLATE.**—For description see U. S. Pharmacopeia under Sodii Cacodylas.

*Actions, Uses and Dosage.*—See Useful Drugs.

*Ampuls Sodium Cacodylate-Mulford 1 1/2 grains.*—Each ampule contains sodium cacodylate 0.1 Gm. (1½ grains). Prepared by H. K. Mulford Co., Philadelphia.

*Ampuls Sodium Cacodylate-Mulford, 3 grains.*—Each ampule contains sodium cacodylate 0.2 Gm. (3 grains). Prepared by H. K. Mulford Co., Philadelphia.

*Ampuls Sodium Cacodylate-Mulford, 7 3/4 grains.*—Each ampule contains sodium cacodylate 0.5 Gm. (7¾ grains.) Prepared by H. K. Mulford Co., Philadelphia.

*Ampuls Sodium Cacodylate-Mulford, 15 grains.*—Each ampule contains sodium cacodylate 1 Gm. (15 grains). Prepared by H. K. Mulford Co., Philadelphia.

*Ampuls Sodium Cacodylate-Squibb, 0.05 Gm.*—Each ampule contains sodium cacodylate 0.05 Gm. (¼ grain) in 1 Cc. of sterile solution. Prepared by E. R. Squibb & Sons, New York.

*Ampuls Sodium Cacodylate-Squibb, 0.13 Gm.*—Each ampule contains sodium cacodylate 0.13 Gm. (2 grains) in 1 Cc. of sterile solution. Prepared by E. R. Squibb & Sons, New York.

**Sodium Cacodylate-Merck.**—A nonproprietary brand complying with the standards for sodium cacodylate.

Merck & Co., New York, distributors.

### Arsenic Compounds, Complex—Organic

**ARSENO-TRIFERRIN.** — *Arsentriferrinum.* — An iron arsenoparanucleate containing arsenic in organic combination and standardized to contain a definite amount of arsenic by diluting with iron paranucleate. It should contain about 16 per cent. of iron, 0.1 per cent. of arsenic (As), and 2.5 per cent. of phosphorus, all in organic combination.

*Actions and Uses.*—Arseno-triferrin passes through the stomach unchanged and undissolved, but is dissolved in the intestines and absorbed. This behavior prevents injurious action of arsenic on the gastric mucous membrane.

Arseno-triferrin is said to be useful in cases of anemia which are rebellious to iron alone, and in neurasthenia, hysteria, and in skin diseases.

*Dosage.*—0.3 Gm. (5 grains) three times a day after meals.

Manufactured by Knoll & Co., Ludwigshafen a/Rh., Germany, and New York (E. Bilhuber, New York, distributor). U. S. trademark No. 36,747.

*Arseno-Triferrin Tablets, 5 grains.*—Each tablet is said to contain arseno-triferrin 0.3 Gm. (5 grains).

*Arseno-Triferrol.*—Elixir Arseno-Triferrini.—An elixir of arseno-triferrin containing in each 4 Cc. (1 fluidrachm) about 0.06 Gm. (1 grain) of arseno-ferrin in a menstruum containing 15 per cent. of alcohol. It

is prepared by dissolving a soluble form of arseno-triferrin in a vehicle consisting of water, alcohol, tincture of orange, compound tincture of cardamom and vanillin.

Arseno-triferrin is an orange-colored, tasteless powder, soluble in dilute alkalis from which it can be precipitated by the addition of an acid. It is also soluble in about 8 per cent. of hydrochloric acid on warming.

The determination of the amount of iron, arsenic and phosphorus in arseno-triferrin is carried out according to the method in "Prüfungsvorschriften für die pharmazeutischen Spezialpräparate." (Knoll & Co.)

**ELARSON.**—Strontium Chlorarsinosobehenolate.—Essentially strontium chlorarsinobehenolate

$(C_8H_{17}.C \equiv C.(CH_2)_{11}.COO)_2Sr$ , with some strontium behen-



olate  $(C_8H_{17}.C \equiv C.(CH_2)_{11}.COO)_2Sr$ , and contains about 13 per cent. of elementary arsenic and about 6 per cent. of chlorin.

*Actions and Uses.*—Elarson has the action of arsenic, but the arsenic, being in lipid-like combination, is said to be much better utilized in the system and to exert its therapeutic effects in smaller doses than other organic arsenical preparations. It also possesses the advantage of being relatively free from irritating action on the gastro-intestinal tract.

Elarson has been employed with excellent effect in anemias due to various causes, such as chlorosis, and seems to be beneficial in diseases of the skin, phthisis, malignant disease, chorea, neuralgias, etc. By its action in improving the condition of the blood it appears to exert a beneficial influence in some cases of epilepsy.

*Dosage.*—The average adult dose of elarson is 0.008 gm. ( $\frac{1}{8}$  grain), three to five times daily, best taken about an hour after meals. Elarson is marketed in the form of tablets only. (See below.)

Manufactured by the Farbenfabriken vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent No. 1,082,509 (Dec. 30, 1913; expires 1930). U. S. trademark No. 91,419.

*Elarson Tablets.*—Each tablet contains elarson equivalent to arsenic 0.0005 Gm. ( $\frac{1}{2128}$  grain).

Elarson is prepared by treating behenolic acid with arsenic trichloride and converting the oily acid thus formed to the solid strontium salt.

According to Fischer (*Ann. d. Chem.* [Liebig's], **403**: 106, 1914) elarson is a mixture of 89.2 per cent. of strontium chlorarsinosobehenolate and 10.8 per cent. of strontium behenolate, the arsenic being present as an arsinoso ( $-AsO$ ) group. The analysis of elarson showed strontium 9.2 per cent.; arsenic 13.18 per cent. and chlorin 6.28 per cent.

Elarson is an almost white, amorphous, tasteless powder, insoluble in water and but slightly soluble in alcohol and ether. When heated it decomposes with evolution of volatile organic substances and elementary arsenic, frothing and turning black.

If elarson is shaken with water (1:20) the filtrate should not change litmus, become turbid on addition of silver nitrate or barium chloride solution nor leave a residue on evaporation. If 2 Gm. of elarson be boiled with 25 Cc. of a 15 per cent. alcoholic solution of potassium hydroxide for about one-half hour, using a reflux condenser, and if to a portion of the alcoholic fluid, which has been diluted with water, diluted sulphuric acid is added and then filtered, half of the filtrate saturated with hydrogen sulphide, should yield a voluminous yellow precipitate of arsenic sulphide. If to the other half of the filtrate nitric acid and silver nitrate solution be added a precipitate of silver chloride should be formed. If the second portion of the alcoholic solution be diluted with water, acidified with dilute hydrochloric acid and filtered, the filtrate should yield a precipitate of strontium oxalate on addition of ammonium hydroxide and ammonium oxalate solutions.

## ATROPINE DERIVATIVES AND ANALOGUES

### Synthetic Mydriatics

The usefulness of atropine is somewhat diminished by the fact that it affects, simultaneously, so many organs; on the eye its effects continue much longer than is, in many cases, desirable. Many attempts have been made to secure drugs of the atropine type with more specific actions or such as have a more transitory effect upon the eye. Of those listed below one (eumydrin) is a derivative of atropine; another (homatropine) is a synthetic alkaloid analogous to atropine, the only difference being that it contains mandelic acid instead of tropic acid in combination with tropine; eupthalmin is a combination of mandelic acid and a base similar to that contained in beta-eucaine.

**HOMATROPINE HYDROCHLORIDE.**—Homatropinæ Hydrochloridum.— $C_{16}H_{21}O_3NHCl$ .—The hydrochloride of the alkaloid homatropine, obtained by the condensation of tropine and mandelic acid.

*Actions and Uses.*—Homatropine hydrochloride is given for the same indications as the hydrobromide, over which, however, it seems to have no advantages.

*Dosage.*—It is applied to the eye in 1 per cent. solution.

Homatropine hydrochloride occurs as small white crystals, soluble in water and alcohol and melting at 216 to 217 C.

The color test for the identification of homatropine hydrochloride and those showing the absence of impurities should agree with those described in the U. S. Pharmacopeia under homatropine hydrobromide.

**Homatropine Hydrochloride - Merck.**—A nonproprietary brand complying with the standards for homatropine hydrochloride.

Merck & Co., New York, distributors.

**Homatropine Hydrochloride-Roche.**—A non-proprietary brand complying with the standards for homatropine hydrochloride.

Manufactured by F. Hoffman-LaRoche and Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York).

### BARIUM SULPHATE FOR ROENTGEN-RAY WORK.

—Barium sulphate freed from soluble barium salts.

*Action, Uses and Dosage.*—Barium sulphate for roentgen-ray work, being freed from soluble barium and other salts, passes through the system unchanged and because of this is used in taking roentgen-ray pictures of the stomach and of the intestines.

*For the Roentgen-Ray Examination of the Stomach.*—The evening before the examination the patient receives 1 fluid-ounce of castor oil. In the morning an ordinary portion of wheat-meal porridge with which 2 ounces of barium sulphate have been well mixed, together with a little sugar and cream, is administered by mouth. The patient is then directed to abstain from further food. The examination is made six hours later.

*For the Roentgen-Ray Examination of the Colon.*—An enema consisting of 16 ounces of mucilage of acacia, 3 pounds of condensed milk, and 8 ounces of barium sulphate is warmed to body temperature and injected into the rectum from a height of from 3 to 6 feet. The examination is made with a fluoroscope while the injection is passing into the rectum.

Barium sulphate for roentgen-ray work is a fine, white odorless, tasteless and relatively light powder, which is insoluble in water and organic solvents as well as in acids and in dilute alkalies.

Boil 10 Gm. of barium sulphate for roentgen-ray work with a mixture of 10 Cc. of acetic acid (Sp. Gr. 1.064) and 90 Cc. of water and filter. Evaporate 50 Cc. of the filtrate on a steam bath to dryness, dissolve the residue in 20 Cc. of water and filter (return the filtrate to the filter until quite clear) and to the filtrate add a few drops of dilute sulphuric acid; no separation of barium sulphate should occur within one-half hour (soluble barium salts or carbonate). Saturate a 25 Cc. portion of the acetic acid extract with hydrogen sulphide: it should not become colored or turbid (heavy metals).

Boil 2 Gm. of barium sulphate for roentgen-ray work for a few minutes with 10 Cc. of nitric acid (Sp. Gr. 1.149 to 1.152) and filter: the filtrate does not give a yellow precipitate with ammonium molybdate solution within half an hour (barium phosphate).

Triturate 2 Gm. of barium sulphate for roentgen-ray work with 10 Cc. of stannous chloride solution: no dark coloration occurs within one-half hour.

**Barium Sulphate-Brady for Roentgen-Ray Work.**—A brand complying with the N. N. R. standards for barium sulphate for roentgen-ray work.

Manufactured by Geo. W. Brady & Co., Chicago.



**Barium Sulphate-P. W. R. for X-Ray Diagnosis.**—A brand complying with the N. N. R. standards for barium sulphate for roentgen-ray work.

Manufactured by Powers-Weightman-Rosengarten Co., Philadelphia.

**Barium Sulphate-Merck for X-Ray Diagnosis.**—A brand complying with the N. N. R. standards for barium sulphate for roentgen-ray work.

Merck & Co., New York, distributors.

**Barium Sulphate-Squibb for Roentgen-Ray Work.**—A brand complying with the N. N. R. standards for barium sulphate for roentgen-ray work.

Manufactured by E. R. Squibb & Sons, New York.

**BENZENE, MEDICINAL.** — *Benzenum Medicinale.* — Medicinal Benzol.—Crystallizable Benzol.— $C_6H_6$ .—A liquid consisting almost entirely of benzene (cyclohexatriene).

*Actions and Uses.*—When swallowed, this drug usually produces a sensation of burning in the stomach. Benzene is a narcotic which, when swallowed or inhaled, produces vertigo, delirium and tonic convulsions followed by deep sleep; the ingestion of 30 Cc. (1 ounce) of nearly pure benzene has proved fatal. In some cases of chronic poisoning petechial spots, due to small hemorrhages, have been observed. These spots have been attributed to fatty degeneration of the blood-vessels. It produces leukocytosis followed by leukopenia with an occasional increased number of erythrocytes. Larger doses may produce an aplastic anemia. It has been stated that the aplastic anemia is due to a contamination of the drug with nitrobenzene or aniline. Benzene has been used occasionally on account of its narcotic properties and has also been used as an intestinal antiseptic. It is, however, rarely used for these purposes at the present time. It has been somewhat extensively used in the treatment of leukemia. Moderate doses cause a rapid destruction of the leukocytes, especially the lymphocytes. This action is accompanied by an improvement in the subjective symptoms and, in some cases, by a marked reduction in the size of the spleen. In many cases the lymphocytes have been reduced to the normal figure. In others the number of leukocytes has still remained high, although the size of the spleen was reduced. In many cases the improvement is such that an apparent cure is produced. However, a large number, if not all, of these patients relapse or succumb to the toxic action of the benzene. The administration of this drug should be stopped before the leukocytes are reduced to the normal level. Benzene has also been used in a few cases of Hodgkin's



disease and in cases of polycythemia. The effect of benzene on the leukocytes is largely enhanced by the previous or simultaneous treatment with the roentgen ray. The value of benzene in leukemia is not established and caution against too large and too long-continued dosage should govern its employment.

*Dosage.*—0.5 to 1 Cc. (8 to 15 minims) given four times a day. Medicinal benzene may be given in capsules or in an emulsion or may be administered by rectum. Frequent examinations of the blood should be made during the administration of medicinal benzene to determine when it is advisable to suspend the administration of the medicine.

Medicinal benzene is prepared by fractional distillation of the light oil of coal tar and is a colorless, mobile liquid, possessing a strong characteristic but not disagreeable odor and a burning taste. It has a specific gravity of from 0.881 to 0.885 at 15 C.

Medicinal benzene is insoluble in water but soluble in 90 per cent. alcohol and in carbon disulphide; it is miscible with absolute alcohol and ether. Medicinal benzene is a solvent for bromine, iodine, sulphur, phosphorus, fatty and volatile oils, rubber, gutta-percha, wax, various resins, a large number of alkaloids and some aromatic acids.

Medicinal benzene boils at from 79 to 82 C. It is inflammable and burns with a luminous and sooty flame. When cooled to 0 C., medicinal benzene solidifies. If cooled slowly it crystallizes in rhombohedral prisms, which melt at about 6 C.

It is neutral toward litmus.

Medicinal benzene is not affected by cold sulphuric acid but is soluble in fuming nitric acid, without liberating nitrous vapors. When poured into water the mixture separates and deposits oily globules of nitrobenzene, which can be identified by its characteristic bitter almond odor.

If 2 Cc. of medicinal benzene be shaken with 0.5 Cc. concentrated sulphuric acid and 1 drop of fuming nitric acid, no green or blue tint should be produced.

**Benzene-Merck, H. P., Crystallizable.**—A nonproprietary brand complying with the standards for benzene, medicinal.

Merck & Co., New York, distributors.

**BENZIDINE.**—Para-diamino-diphenyl.—For description see the U. S. Pharmacopeia under Reagents and Test Solutions.

**Benzidine-Merck (For Blood Test).**—A nonproprietary brand complying with the standards for benzidine.

Merck & Co., New York, distributors.

**Occult Blood Test (Dudley Roberts).**—This consists of tablets each containing 5 grains of a trituration of benzidine, 1 part, and sodium perborate, 20 parts, and glacial acetic acid (supplied in boxes containing 100 tablets in vials, and a bottle of glacial acetic acid).

*Actions, Uses and Dosage.*—A tablet is placed in a small saucer or other suitable container; to it is added a quantity of the material to be tested (a weak solution of the stool or stomach contents, or urine), sufficient to wet thoroughly, but not to cover the tablet entirely, and then a drop or two of the acetic acid is allowed to fall on the tablet; if blood is present the tablet will turn greenish blue, the extent of the coloration and the time of its development depending on the amount of blood present. (To avoid contamination of the glacial acetic acid remaining in the bottle, care should be taken not to touch the tablet or specimen with the rod which is used to transfer the acetic acid for the test.)

Prepared by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

**BENZYL ALCOHOL.**—Phenmethylo $\text{l}$ .— $\text{C}_6\text{H}_5\text{CH}_2\text{OH}$ .—An aromatic alcohol occurring as an ester in tolu and other balsams, produced synthetically.

*Actions and Uses.*—Benzyl alcohol is now being used as a local anesthetic by injection and on mucous membranes. It is said to be practically nonirritant and nontoxic in the ordinary concentrations and doses.

*Dosage.*—Benzyl alcohol is usually used in the form of a 1 to 4 per cent. solution in water or physiologic sodium chloride solution. Such solutions may be sterilized by boiling, without danger of decomposition. Pure benzyl alcohol is markedly antiseptic. The technic of injection is the same as for other local anesthetics.

Benzyl alcohol is a colorless liquid with a faint aromatic odor, and a sharp burning taste. When placed on the tongue it produces numbness, even in very small quantities. It is soluble, 1 Cc. in 25 Cc. water, and miscible in all proportions with alcohol, ether, and chloroform.

Benzyl alcohol boils without decomposition between 200 and 206 C. When ignited it burns with a smoky flame.

It has a specific gravity of from 1.040 to 1.050 at 15 C., and 1.032 to 1.042 at 25 C.

Benzyl alcohol is neutral to litmus. If 2 or 3 drops are added to a strong solution of potassium permanganate acidulated with sulphuric acid, rapid oxidation takes place and the odor of benzaldehyde is plainly evident. On heating the mixture further oxidation takes place and then by adding dilute sulphuric acid and decolorizing the mixture with hydrogen dioxide, benzoic acid may be obtained by extracting with ether.

Wind the end of a copper wire to a spiral about  $\frac{1}{4}$  inch in diameter and length, hold this spiral in a nonluminous flame until no green coloration is imparted to the latter. Fill the spiral with a few drops of benzyl alcohol and let these burn off outside the flame. Place the nonluminous flame against a dark background and hold the loop in the right or left margin of the flame. Not even a transient green coloration should be imparted to the latter.

If 5 Cc. are shaken with 5 Cc. sodium hydroxide solution (5 per cent.) and allowed to stand one hour, no yellow color should appear in the aqueous layer (*aldehyde*).

One volume of benzyl alcohol should dissolve in 1.5 volumes of 50 per cent. alcohol.

Ten Cc. benzyl alcohol should leave no weighable residue on evaporation and heating until all carbon is burned away.

**Phenmethylol-H. W. & D.**—A nonproprietary brand of benzyl alcohol complying with the tests and standards for benzyl alcohol.

Manufactured by Hynson, Westcott & Dunning, Baltimore, Md.

*Phenmethylol Ampules, 1 per cent.-H. W. & D.*—Ampules containing 5 Cc. of a sterile solution of phenmethylol-H. W. & D. 1 Gm., in physiological sodium chloride solution 99 Gm.

*Phenmethylol Ampules, 2 per cent.-H. W. & D.*—Ampules containing 5 Cc. of a sterile solution of phenmethylol-H. W. & D. 2 Gm., in physiological sodium chloride solution 98 Gm.

*Phenmethylol Ampules, 4 per cent.-H. W. & D.*—Ampules containing 5 Cc. of a sterile solution of phenmethylol-H. W. & D. 4 Gm., in physiological sodium chloride solution 96 Gm.

**BENZYL BENZOATE.**—Benzylis Benzoas.— $C_6H_5COO.C_6H_5CH_2$ .—The benzyl alcohol ester of benzoic acid. It contains not less than 95 per cent. benzyl benzoate.

*Actions and Uses.*—Benzyl benzoate lowers the tone of unstriated muscle, and has been suggested as a remedy against renal, biliary, uterine, and intestinal colic and other spasms of smooth muscle, including angiospasm. Its clinical use is still in the experimental stage.

*Dosage.*—0.3 to 0.5 Cc. (5 to 7 minims).

Benzyl benzoate is a colorless oily liquid above about 20 C. It is odorless, or has a faint aromatic odor, and a sharp burning taste. It is insoluble in water or glycerin but miscible in all proportions with alcohol, chloroform and ether.

Benzyl benzoate boils at 340 to 350 C. with partial decomposition. When ignited it burns with a very smoky flame.

Specific gravity 1.09 to 1.13 at 15 C., 1.083 to 1.122 at 25 C.

Benzyl benzoate is neutral to litmus. It is readily saponified by alcoholic solution of potassium hydroxide. The solution obtained when neutralized yields a flesh-colored precipitate with ferric chloride solution, and upon acidulation a white crystalline precipitate of benzoic acid separates. This precipitate may be identified by extracting with ether and applying the usual tests for benzoic acid.

Ten Cc. benzyl benzoate should leave no weighable residue upon evaporation and heating until all carbon is burned away. To about 2 Gm. benzyl benzoate, accurately weighed, add 25 Cc. half-normal alcoholic potassium hydroxide solution and heat the mixture to incipient boiling under a reflux condenser for one hour. To the cooled solution add phenolphthalein and titrate the excess potassium hydroxide with half-normal hydrochloric acid. The volume of half-normal potassium hydroxide used should indicate not less than 95 per cent. benzyl benzoate (each Gm. benzyl benzoate requires for saponification not less than 8.9 Cc. or more than 9.4 Cc. half-normal alcoholic potassium hydroxide solution).

**Benzyl Benzoate-H. W. and D.**—A nonproprietary brand of benzyl benzoate complying with the tests and standards for benzyl benzoate.

Manufactured by Hynson, Westcott and Dunning, Baltimore, Md.

*Solution of Benzyl Benzoate, Miscible-H. W. and D.*—A solution of 20 Gm. benzyl benzoate in 78 Gm. ethyl alcohol to which is added 2 Gm. of powdered castile soap as an emulsifying agent.

*Actions and Uses.*—Same as benzyl benzoate.

*Dosage.*—1.5 to 2 Cc. (20 to 30 minims).

**BERBERINE HYDROCHLORIDE.**—*Berberinæ Hydrochloridum.*— $C_{20}H_{17}NO_4 \cdot HCl + 2H_2O$ .—The hydrochloride of an alkaloid obtained from *Hydrastis canadensis* and *Berberis vulgaris*.

*Actions and Uses.*—Given by mouth, berberine hydrochloride acts like other bitter drugs in the stomach. Very large doses, although not fatal, cause diarrhea, tremor, general weakness, low blood-pressure (from depression of vasomotor center and of cardiac muscle), rapid pulse (depression of vagus endings) and quickened respiration. Recovery is slow. Nephritis may be present. Subcutaneous injection kills by paralysis of respiration, with symptoms of asphyxia and paralysis. This drug has been used as a bitter tonic, for diarrhea, the vomiting of pregnancy and as a febrifuge.

*Dosage.*—From 0.06 Gm. to 0.3 Gm. (1 to 5 grains). As much as 20 grains have been taken without obvious effect other than a loose stool.

Berberine hydrochloride occurs as bright yellow, acicular crystals or amorphous powder. It is slightly soluble in alcohol to which it imparts a deep yellow color. It is soluble in 300 parts cold water, but dissolves more easily in hot water.

An aqueous solution of berberine or its salts treated with chlorine or bromine water produces a blood-red color. Bromine water in excess precipitates the reddish-brown berberine tetrabromide hydrobromide— $C_{20}H_{17}NO_4 \cdot Br_4 \cdot HBr$ , which is converted by washing with alcohol or heating to 100 C. to the yellow-brown berberine dibromide-hydrobromide  $C_{20}H_{17}NO_4 \cdot Br_2 \cdot HBr$ . Ammonium sulphide precipitates from an alcoholic solution of berberine hydrochloride the polysulphide  $(C_{20}H_{17}NO_4)_2H_2S_6$ , which crystallizes in brown-black needles. Berberine solutions, even if very dilute, when treated with potassium iodide solution yield a yellow precipitate of berberine hydriodide.

**Berberine Hydrochloride-Merck.**—A nonproprietary brand complying with the standards for berberine hydrochloride.

Merck & Co., New York, distributors.

## BILE SALTS AND BILE SALT COMPOUNDS

The bile of man and of several animals contains the sodium salts of conjugated cholic acids in varying proportions; in ox and human biles especially glycocholic acid,  $C_{26}H_{45}O_6N$ ; and taurocholic acid,  $C_{26}H_{45}O_7NS$ . Fresh ox-gall is said to contain about 3 per cent. each of sodium glycocholate and sodium taurocholate.

*Actions and Uses.*—The bile salts constitute the main active principles of bile, and therefore share the actions and uses of the latter, perhaps with the advantage of more constant composition. When injected into the circulation they cause severe nervous and cardiac depression, not observed when they are given by the mouth. They are generally credited with a slight antiseptic and laxative action, with enhancing



the efficiency of the resinous hydragogue cathartics, and with emulsifying and hence favoring the absorption of fat. They stimulate the secretory activity of the liver, increasing both the fluids and solids of the bile. While they are regarded as the most powerful of the so-called cholagogues, it is doubtful whether their effect is very pronounced.

They have been used in obstructive jaundice, although the rationale is somewhat doubtful; their use in biliary fistula is more reasonable, if the nutrition is noticeably affected.

The sodium glycocholate and taurocholate may be separated in the following manner: Dry ox-bile is treated with absolute alcohol and the tincture precipitated by ether in excess. Both salts are deposited and the glycocholate crystallizes on standing, the taurocholate remaining in amorphous form, resembling oily or resinous matter. If the deposit be dissolved in water, solution of lead acetate will throw down a lead glycocholate, while the addition of lead subacetate to the remainder will precipitate the taurocholate.

Tests: All the bile acids respond to Pettenkofer's test. A small portion of the salt is dissolved in a little concentrated sulphuric acid in a small porcelain dish and warmed, care being taken that the temperature does not rise higher than 60 to 70 C. A 10 per cent. solution of cane sugar is then added drop by drop while the liquid is stirred with a glass rod. If compounds of cholic acid are present a beautiful red color will appear, which does not disappear at room temperature, but usually in the course of a day becomes bluish violet. The red liquid shows in the spectrum two absorption bands, one at F and the other between D and E near to E. Care must be taken not to heat too much or to add too much sugar. The sulphuric acid must be free from sulphurous acid and the lower oxides of nitrogen. As albumin, oleic acid, amyl alcohol, morphine, etc., may give a similar reaction, spectroscopic examination should not be omitted in doubtful cases (Hammarsten, *Lehrbuch der physiolog. Chemie*, Ed. 6, p. 312). Furfural Test (Mylus): The substance is dissolved in alcohol and for every cubic centimeter of the alcoholic solution, 1 drop of a 1:1000 furfural solution and 1 Cc. of concentrated sulphuric acid are added and the mixture cooled, if necessary, so that the temperature may not rise too high. The same color reaction occurs as in Pettenkofer's test.

**BILEIN.**—Sodii Glyco-Taurocholas Bovis-Abbott.—A mixture of the essential salts of the bile.

*Actions and Uses.*—See general article above, Bile Salts and Bile Salt Compounds.

Manufactured by the Abbott Laboratories, Chicago. U. S. trademark No. 44,140.

*Bilein Pills, 1/4 grain.*—Each pill contains bilein 0.015 Gm. (¼ grain).

*Bilein Pills, 1/8 grain.*—Each pill contains bilein 0.008 Gm. (⅛ grain).

*Bilein Pills, 1/12 grain.*—Each pill contains bilein 0.006 Gm. (⅓ grain).

**BILE SALTS-FAIRCHILD.**—A preparation obtained from fresh ox-gall, consisting essentially of sodium glycocholate

and sodium taurocholate, in the proportion existing in ox-bile.

*Actions and Uses.*—See general article above, Bile Salts and Bile Salt Compounds.

*Dosage.*—From 0.125 to 0.4 Gm. (2 to 6 grains), from 4 to 5 Gm. (60 to 75 grains), per day.

Manufactured by Fairchild Bros. & Foster, New York.

**GLYCOTAURO.**—Bile Salts-H. W. & D.—Concentrated ox-bile, freed from bile pigments, standardized to contain 50 per cent. of the natural mixture of sodium glycocholate and sodium taurocholate. Each Gm. represents approximately 15 Cc. of fresh ox-bile.

*Actions and Uses.*—See general article above, Bile Salts and Bile Salt Compounds.

Manufactured by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

*Glycotauro Capsules, 5 grains.*—Each capsule contains glycotauro 0.3 Gm. (5 grains).

*Glycotauro Capsules (half size).*—Each capsule contains glycotauro 0.15 Gm. (2½ grains).

*Enteric Coated Glycotauro Tablets.*—Each tablet contains glycotauro 2 grains and is coated with salol.

Glycotauro is prepared by evaporating ox-bile in presence of animal charcoal, extracting the residue with purified methyl alcohol, filtering, evaporating the filtrate and mixing the residue with glycerin.

Glycotauro is a soft semisolid mass of light brown color, bile-like odor and slightly bitterish taste. It is easily soluble in water and alcohol. Its specific gravity is about 1.22.

**OVOGAL.**—Albumen Cholicum.—A combination of bile acids with egg albumin.

*Actions and Uses.*—Ovogal is said to pass the stomach without marked decomposition and to be dissolved and absorbed in the intestine.

For therapeutic indications see general article above, Bile Salts and Bile Salt Compounds.

*Dosage.*—0.5 to 1 Gm. (8 to 15 grains) several times daily in capsules with water, tea, coffee or fruit juices.

Manufactured by J. D. Riedel Aktiengesellschaft, Berlin, Germany (Riedel & Co., New York). No U. S. patent. German patent No. 176,945. U. S. trademark No. 78,352.

*Ovogal Capsules.*—Each capsule is said to contain ovogal 0.5 Gm. (7½ grains).

Ovogal is a greenish-yellow powder, insoluble in water, dilute acids, ether, benzol, fats, etc. Alcohol and acetone do not dissolve it, but after long action remove from it small amounts of the bile acids. Alkalies dissolve ovogal, splitting it into albumin and bile acids (glycocholic and taurocholic acid).

If 0.5 Gm. of ovogal is boiled with 1 to 2 Cc. hydrochloric acid until a clear green solution is produced and then diluted with from 30 to 40 Cc. of absolute alcohol an abundant cloudy precipitate separates, which when washed with alcohol until the washings are colorless, gives the characteristic reactions for proteins. On evaporation of the alcoholic filtrate, the bile acids may be recovered and identified. Ovogal on ignition should leave no weighable residue.

## BISMUTH COMPOUNDS

The insoluble compounds of bismuth have, for the most part, a mechanical action as protectives of inflamed or irritated surfaces. On a wound a fine crust is formed, beneath which healing proceeds as beneath a scab. The antiseptic action plays a secondary rôle, the drying property of the powder being of the chief importance. For the best development of the protective mechanical action a very fine division of the bismuth compound is essential. This has been secured in various ways. Soluble complex salts of bismuth, being decomposed by dilute mineral acids with precipitation of insoluble bismuth salt in a very fine state of subdivision, are administered with the expectation that the gastric juice will bring about the desired reaction. It is questionable whether this assumption is realized in many cases. Pharmacologists and many clinicians doubt the usefulness of all soluble bismuth preparations. On the other hand, the powder is given alone or prepared in a permanent suspension holding the bismuth in such fine state of division as to favor its deposition evenly throughout the whole intestinal tract.

Bismuth has been combined with other substances either in mixture or in synthetic compounds, for securing convenience in administration, or with the aim of enhancing its protective and antiseptic action. It is doubtful if combination with antiseptic acids, as in bismuth subgallate or bismuth subsalicylate, increases the efficiency of the preparation. The antiseptic acids lose their power in alkaline liquids, as in the intestines; the introduction of iodine into the acid radical does not increase the antiseptic power. On the other hand, bismuth compounds with phenol or with phenols in which bromine or iodine has replaced hydrogen in the benzene ring have an antiputrefactive action.

*Toxic Effects.*—Soluble compounds of bismuth should be used with caution because of the danger of absorption of poisonous amounts of bismuth. Absorption of insoluble bismuth compounds from wounds and cavities occasionally occurs. Bismuth poisoning is indicated by a blue line on the gums, headache, nausea and stomatitis. Removal of the bismuth application is the principal treatment. Too free application of bismuth-containing powders or too free injection into cavities should be avoided. Large doses of bismuth subnitrate have produced nitrite poisoning by their reduction in the colon.

*Classes of Bismuth Compounds.*—The compounds of bismuth are here divided into soluble and insoluble. The soluble compounds are bismon, a colloidal bismuth oxide, and two scale compounds, one in which bismuth is combined with iron citrate and the other containing lithium citrate. These mixtures are suited only to special cases and have little advantage over the separate prescription of several ingredients.

The insoluble compounds include airol, bismuth subgallate, in which the bismuth is combined with an antiseptic acid which probably adds nothing to its antiseptic power; on the other hand, bismuth betanaphtholate and bismuth tribromphenate are phenolic compounds which may reasonably be expected to have some antiseptic power. (See Fränkel, *Arzneimittel Synthese*, Ed. 3, p. 634).

### Bismuth Compounds, Soluble

**BISMON.**—Colloidal Bismuth Oxide.—A preparation of colloidal bismuth meta-hydroxide equivalent to about 20 per cent. metallic bismuth.

*Actions and Uses.*—Bismon has the actions of other preparations of bismuth, but it is claimed that, on account of its solubility (property of forming colloidal suspension) it is more rapidly distributed over the mucous membrane of the gastro-intestinal tract.

It is said to be useful in acute and chronic intestinal derangements and in various forms of dyspepsia in infants and young children.

*Dosage.*—0.5 Gm. (8 grains) in 5 to 10 per cent. solution (colloidal suspension) in water. The solution (colloidal suspension) may be added to milk or other appropriate liquid food.

Manufactured by Kalle & Co., A. G., Biebrich a/Rh., Germany. (Kalle Color & Chemical Co., Inc., New York). Trademarked in Germany. No U. S. patent or trademark.

It is stated that bismon results from the action of sodium lysalbinat and sodium protalbinat on bismuth salts.

Bismon is a light brown granular substance, forming, with water, a fairly stable opalescent colloidal suspension (in these suspensions colloidal bodies are in such extreme state of subdivision that they were formerly supposed to be in solution and are still commonly so considered). In aqueous suspensions, decomposition manifested by the appearance of a black deposit is said to set in after three to four weeks. The aqueous suspension is not affected by metals.

If an aqueous solution of egg albumin be added drop by drop to a 1 per cent. aqueous suspension of bismon a white precipitate forms, which is soluble in an excess of the albumin solution. If hydrochloric acid be added to an aqueous suspension of bismon a white turbidity appears, which is soluble in an excess of the acid. If hydrogen sulphide be passed into a 1 per cent. suspension of bismon a dark brown color, but no precipitate, is formed. The addition of acid to



this suspension produces a brown precipitate. Bismon, when heated, chars, with evolution of fumes of burning nitrogenous matter, yielding finally a residue, which when dissolved in nitric acid responds to tests of identity for bismuth. If 1 Gm. bismon be gradually heated with fusion mixture, until all carbonaceous matter has been destroyed, the fused mass when cooled, dissolved in nitric acid, the bismuth precipitated with ammonium carbonate solution, the resulting precipitate when ignited to constant weight should yield at least 0.2128 Gm. bismuth oxide ( $\text{Bi}_2\text{O}_3$ ) corresponding to 19.7 per cent. bismuth.

**BISMUTH AND IRON CITRATE (SOLUBLE), Wellcome Brand.**—Bismuthi et Ferri Citras-Wellcome.—A “scale salt” containing bismuth citrate and ferric citrate in amounts corresponding to from 38 to 40 per cent. each of the respective anhydrous salts (corresponding to 20 to 21 per cent. bismuth and 8.7 to 9.1 per cent. iron), the combination being rendered soluble in water by means of ammonia.

*Actions and Uses.*—This preparation has the properties of iron and soluble bismuth salts. Its administration is proposed by the manufacturer in cases of dyspepsia accompanied by anemia, in order that the sedative action of bismuth may be exerted on the digestive organs, while the iron may combat the anemia.

*Dosage.*—From 0.3 to 0.65 Gm. (5 to 10 grains).

Manufactured by Burroughs Wellcome & Co., London and New York. No U. S. patent or trademark.

Bismuth and iron citrate (soluble) occurs in yellowish-green scales, readily soluble in water, having a saline, mildly ferruginous taste.

A solution of bismuth and iron citrate (soluble) is acid toward litmus; addition of dilute acids or of ammonia water renders the solution darker, but does not cause precipitation; addition of sodium hydroxide test solution causes formation of a reddish-brown precipitate and evolution of ammonia. The iron content of bismuth and iron citrate (soluble) may be determined by the methods prescribed for ferri et ammonii citras U. S. P. The amount of bismuth is determined by precipitating by hydrogen sulphide from an acid solution, dissolving the bismuth sulphide obtained in dilute nitric acid, precipitating the bismuth from this solution by ammonium carbonate and weighing as bismuth oxide.

**BISMUTH AND LITHIUM CITRATE (SOLUBLE), Wellcome Brand.**—Bismuthi et Lithii Citras Solubilis-B. W. & Co.—A “scale salt” of bismuth and lithium citrate containing 40 to 45 per cent. of bismuth (Bi) and 2.5 to 3 per cent. of lithium.

*Actions and Uses.*—This preparation is recommended by the manufacturers as a convenient form of medication when the effects of both lithium and bismuth are desired, as in gouty dyspepsia.

*Dosage.*—From 0.125 to 0.3 Gm. (2 to 5 grains).

Manufactured by Burroughs Wellcome & Co., London, England, and New York. No U. S. patent or trademark.

Bismuth and lithium citrate (soluble) occurs in colorless scales, readily soluble in water. Its aqueous solution is acid toward phenolphthalein, but alkaline toward litmus, test solution.

If 1 Gm. of the salt is warmed with 10 Cc. potassium hydroxide no ammonia is evolved (absence of ammonium compounds).

### Bismuth Compounds, Insoluble

**AIROL.**—Bismuth Iodosubgallas.—Bismuth Oxyiodogallate.—Airoform.— $C_6H_5(OH)_3[COOBiI(OH)]$ .—A combination of bismuth oxyiodide (subiodide) and gallic acid.

*Actions and Uses.*—As airof liberates iodine in the presence of wound secretion it is said to be useful as a substitute for iodoform in the treatment of wounds, burns, skin diseases, gonorrhea, etc.

*Dosage.*—It is used externally in the pure state or diluted with talc, or in the form of a 10 per cent. suspension in equal parts of glycerin and water, or as a 10 to 20 per cent. ointment with 2 parts of petrolatum and 7 parts of wool fat.

Manufactured by F. Hoffman-LaRoche & Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York). U. S. patent expired. German patent Nos. 80,399 and 82,593.

Airol is prepared by heating molecular quantities of bismuth subgallate and hydriodic acid or bismuth oxyiodide and gallic acid, in the presence of water, until a grayish-green product results, which is drained and dried.

It is a voluminous grayish-green, odorless and tasteless powder, insoluble in alcohol, ether, chloroform and olive oil, slightly soluble in glycerin. It is practically insoluble in water, communicating to water a red color on standing, slowly in the cold, but readily when heated, being decomposed with liberation of iodine and bismuth subgallate. It is readily soluble with decomposition, in dilute alkalis and mineral acids. It is decomposed on exposure to moist air, turning red, but in admixture with glycerin and a little water it long remains unaltered.

Airol may be identified by the appropriate tests for its components.

It is incompatible with water and calomel. It should not be exposed to moist air.

**BISMUTH BETANAPHTHOLATE.**—For description see U. S. Pharmacopeia under Bismuthi Betanaphtholas.

**Bismuth Betanaphtholate-Merck.**—A nonproprietary brand complying with the standards for bismuth betanaphtholate.

Merck & Co., New York, distributors.

**Bismuth Betanaphtholate-Mulford.**—A nonproprietary brand complying with the standards for bismuth betanaphtholate.

Manufactured by H. K. Mulford Co., Philadelphia.

*Tablets Bismuth Betanaphtholate-Mulford, 5 grains.*—Each tablet contains bismuth betanaphtholate-Mulford, 0.3 Gm. (5 grains).

Obtained by precipitating a solution of sodium betanaphtholate with an acetic acid solution of bismuth nitrate, with addition of sodium hydroxide solution.

**Orphol-von Heyden.**—A nonproprietary brand complying with the standards for bismuth betanaphtholate.

Manufactured by the Chemische Fabrik von Heyden, Radebeul, near Dresden, Germany (Schering & Glatz, Inc., New York). U. S. patent expired.

*Orphol Tablets.*—Each tablet contains orphol, 0.3 Gm. (5 grains).

**BISMUTH TRIBROMPHENATE.**—**Bismuthi Tribromphenas.**—**Bismuth Tribromphenol.**—**Xeroform.**—A basic bismuth tribromphenate of variable composition.

*Actions and Uses.*—Bismuth tribromphenate is claimed to be a nonirritant and nontoxic antiseptic. It is said to be useful as an odorless and efficient substitute for iodoform; as valuable in ulcer cruris and all weeping eczemas; internally, in gastro-intestinal catarrh, proctitis, dysentery, bacillary and choleraic diarrhea, cholera infantum, etc.

*Dosage.*—From 1 to 3 Gm. (15 to 45 grains) per day to adults; from 0.125 to 0.3 Gm. (2 to 5 grains) at a dose to children. Externally (as a dusting powder, in bandages, etc.) like iodoform.

An amorphous, yellow, nearly odorless and tasteless powder, neutral to moistened litmus paper.

It is only slightly soluble in water, alcohol, chloroform, liquid petrolatum and vegetable oils. Alkalies and strong acids decompose it. It is stable at temperatures below 120 C.

When about 1 Gm. of the salt is boiled with 10 Cc. of sodium hydroxide test solution, the liquid filtered, and the filtrate acidulated with sulphuric acid, the white curdy precipitate produced, when washed and dried, melts at 90 to 95 C. (*tribromphenol*). The contents of the filter dissolve completely in dilute hydrochloric acid (*insoluble inert material*).

Boil 1 Gm. of bismuth tribromphenate with 20 Cc. of a mixture of equal parts of acetic acid and distilled water, cool the solution and filter. Free the filtrate from bismuth by the addition of hydrogen sulphide, boil the mixture and again filter. The latter filtrate leaves not more than 0.005 Gm. of residue on evaporation and gentle ignition (*alkalies and alkali earths*).

Shake for one minute in a separatory funnel, 2 Gm. of bismuth tribromphenate, 20 Cc. of ether, and 20 Cc. of a mixture of equal volumes of hydrochloric acid and distilled water. Draw off the aqueous portion and concentrate to about 4 Cc.; pour it into 100 Cc. distilled water, filter, evaporate the filtrate on the water bath to 30 Cc., again filter and divide this filtrate into portions of 5 Cc. each. Mix one portion with an equal volume of dilute sulphuric acid; it does not become cloudy (*lead*). Treat another portion with a slight excess of ammonia water; the supernatant liquid does not exhibit a bluish tint (*copper*). Another portion is not immediately effected by barium nitrate test solution (*sulphate*).

Heat gently a mixture of about 0.2 Gm. of bismuth tribromphenate with 5 Cc. of potassium hydroxide test solution and about 0.2 Gm. of aluminum wire; the vapors evolved do not turn red litmus blue (*nitrates*).

Shake 1 Gm. of bismuth tribromphenate frequently during fifteen minutes with 30 Cc. of alcohol (95 per cent.), filter and rinse flask with two separate 10 Cc. portions of alcohol, allowing the washings to run through filter. To the combined filtrate and washings add 20 Cc. of tenth-normal sodium hydroxide and a few drops of phenolphthalein solution and determine the excess of alkali with tenth-normal hydrochloric acid. Not more than 1 Cc. of tenth-normal sodium hydroxide should have been consumed by the alcoholic liquid (*free tribromphenol*).

Add 2 Cc. of nitric acid to 2 Gm. of bismuth tribromphenate in a porcelain crucible, carefully evaporate to dryness on a sand bath and incinerate. Dissolve the residue in 5 Cc. of concentrated hydrochloric acid and add to the solution 10 Cc. of a saturated solution of stannous chloride in concentrated hydrochloric acid. The mixture should not darken on standing thirty minutes (*arsenic*).

Mix 0.5 Gm. of the salt with 10 Cc. of a mixture of equal parts of hydrochloric acid, U. S. P. and distilled water. No effervescence should occur (*carbonate*).

To about 0.5 Gm. of bismuth tribromphenate, accurately weighed, add 20 Cc. of hydrochloric acid and digest on water bath. Add 150 Cc. of distilled water and filter. Rinse the beaker with 30 Cc. of distilled water and allow the washings to run through the filter. Saturate the combined filtrate and washings with hydrogen sulphide, filter off the bismuth sulphide, wash and dissolve in hot dilute nitric acid. Add a slight excess of ammonia water followed by 2 Cc. of ammonium carbonate test solution. Allow to stand thirty minutes, filter off the precipitated bismuth hydroxide and heat to constant weight at dull red heat. The residue of bismuth oxide ( $\text{Bi}_2\text{O}_3$ ) should be not less than 45 per cent. nor more than 55 per cent. of the original weight of bismuth tribromphenate taken, corresponding to not less than 40 per cent. nor more than 49 per cent. of bismuth.

**CREMO-BISMUTH.**—*Mistura Bismuthi Subcarbonatis Hydrati-Mulford.*

*Dosage.*—From 4 to 15 Cc. (1 to 4 fluidrachms) every two or three hours.

Prepared by the H. K. Mulford Co., Philadelphia. U. S. trademark No. 29,335.

Cremo-bismuth is a mixture said to consist of bismuth subcarbonate suspended in water in a finely divided state, each 100 Cc. representing the equivalent of 8.66 Gm. (40 grains in one fluidounce) of bismuth subnitrate.

**CRURIN PURUM.**—*Quinolin-Bismuth Sulphocyanate.*—The sulphocyanate of quinolin and bismuth, approximately  $(\text{C}_6\text{H}_7\text{N.HSCN})_3\text{Bi}(\text{SCN})_3$ .

*Actions and Uses.*—Crurin purum is said to be antiseptic. It is used as a local application in gonorrhea and also in the treatment of ulcers of the leg.

*Dosage.*—It is to be used in 1 to 200 watery glycerin emulsion. This should be carefully prepared so that the bottom layer shall resemble milk of sulphur and shall not present a reddish color or maintain any red particles. The injections may be made twice daily and retained for from three to five minutes.



Manufactured by Kalle & Co., A. G. Biebrich a/Rh., Germany (Kalle Color & Chemical Co., Inc., New York). German patent No. 86,148. Trademarked in Germany. No U. S. patent or trademark.

*Crurin Dusting-Powder*.—A preparation said to contain equal parts of crurin purum and starch.

Crurin purum is a fine, brick-red, crystalline powder, with a slight odor of quinolin, insoluble in alcohol and ether, but soluble in acetone and slightly so in pure glycerin. It is decomposed by water with formation, it is stated, of soluble quinolin sulphocyanate or bismuth hydroxide. In the absence of moisture the compound may be kept for a long time unchanged.

When crurin purum is decomposed by water there is formed an insoluble yellow compound and a solution which responds to tests for sulphocyanate in that it yields a deep red color with ferric chloride and a white precipitate with silver nitrate solution, and to tests for quinolin, in that treatment with iodine in potassium iodide solution yields a reddish-brown precipitate insoluble in hydrochloric acid; with picric acid solution it yields a yellow precipitate; with potassium ferrocyanide solution a green precipitate is formed, and with potassium mercuric iodide solution it yields a reddish-yellow precipitate, which dissolves on heating. The yellow insoluble compound, when treated with potassium iodide solution, becomes orange colored, and it responds to tests for bismuth.

Crurin purum treated with dilute nitric acid dissolves with formation of a solution from which bismuth can be separated by precipitation with hydrogen sulphide for quantitative estimation and in which the sulphocyanate content can be determined by titration with standardized silver nitrate solution.

**LAC BISMO.**—*Mistura Bismuthi-Hart*.—A mixture said to consist of bismuth hydroxide and bismuth subcarbonate, suspended in water, in a finely divided state, and containing 0.15 Gm. ( $2\frac{1}{2}$  grains) of the salts in 4 Cc. (1 fluidrachm).

*Dosage*.—From 4 to 15 Cc. (1 to 4 fluidrachms).

Prepared by E. J. Hart & Co., Ltd., New Orleans. U. S. trademark.

## BROMINE DERIVATIVES

Synthetic compounds containing bromine have been produced with the purpose of securing the sedative action of bromine without the objectionable effects of the alkali bromides. These compounds split off bromine ions in the system, the decomposition being due to the oxidation of the organic substance with which it is combined. Too rapid evolution of the bromine is undesirable, while, on the other hand, bromine which is too firmly fixed may fail to become active at all. As the usual indications for bromine action in the organism require a prompt and powerful action on the cells to produce sleep, to abolish reflexes or to arrest an epileptic paroxysm, the synthetic compounds are apt to fail as substitutes for the alkali bromides because their bromine is too slowly evolved. The introduction of bromine into compounds already possessing hypnotic or sedative powers may result in increasing the efficiency of these compounds.

The following bromide derivatives, acting as whole molecule, and therefore devoid of true bromide action, are included in N. N. R.:

Adalin, bromdiethyl-acetyl-carbamide,  $C(C_2H_5)_2Br.CONH.CONH_2$

Brometone, tribrom-tertiary-butyl alcohol,  $CBr_3.C(OH).(CH_3)_3$

Bromural 2-monobrom-isovaleryl-urea,  $CH_3.CH(CH_3).(CHBr.CO)HN.CO.NH_2$

**ADALIN.**— $C(C_2H_5)_2Br.CONH.CONH_2$ . — Bromdiethyl-acetylcarbamide.

*Actions and Uses.*—Adalin is said to be an efficient and prompt sedative, reducing excitement and promoting sleep in conditions in which a powerful hypnotic is not required. In therapeutic doses it is said not to exert any unfavorable influence on the respiration or heart action. The sleep produced is said to be restful, dreamless and exceptionally free from unpleasant by-effects and sequelæ.

Adalin is stated to be useful as a sedative and mild hypnotic in neurasthenia, hysteria, cardiac neuroses with tachycardia, chorea, mental disorders with moderate excitement, insomnia due to various internal diseases, etc.

*Dosage.*—As a sedative from 0.3 to 0.6 Gm. (5 to 10 grains), given in cold water, repeated three or four times daily if necessary: as a hypnotic from 0.6 to 1.3 Gm. (10 to 20 grains), followed by a drink of hot, sweetened water or weak tea.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent No. 983,425 (Feb. 7, 1911; expires 1925). U. S. trademark No. 81,136.

Adalin is prepared by the action on urea of brom-diethyl-acetyl bromide, obtained by the action of bromine on diethylacetic acid anhydride.

Adalin is an almost colorless and odorless crystalline powder, with a melting point of 116 C., which dissolves readily in alcohol as well as in the other ordinary organic solvents. It is soluble with difficulty in water.

**BROMETONE.**—Tribrom-Tertiary-Butylalcohol. — Acetone-Bromoform.— $CBr_3.C(OH).(CH_3)_3$ . — 1,1,1-tribrom-2-methyl-propan-2-ol produced by the reaction of acetone on bromoform.

*Actions and Uses.*—Brometone is claimed to have the sedative action of the bromides without the disadvantage of producing bromism. In doses of 0.3 Gm. (5 grains) four or five times a day, in adults, it is claimed to cause no unpleasant results and to produce no disturbance of the digestive organs, to have no appreciable effect on the secretions. Its action is prompt and its effect is manifest for several hours. In doses exceeding 1.6 Gm. (25 grains) daily it may produce

dizziness, vertigo, anorexia and mental hebetude, all of which symptoms disappear on discontinuance of its use. Therapeutically this drug has been said to be useful in mild conditions of excitation and insomnia, in so-called narcotic abstinence, in hysteria, and in nervous affections generally. It relieves some forms of cough and is said to produce amelioration in some cases of epilepsy. It has been used to relieve dizziness due to labyrinthine disturbances.

*Dosage.*—The dose is 0.3 Gm. (5 grains), dry or in capsules, to be repeated two or three times during twenty-four hours.

Manufactured by Parke, Davis & Co., Detroit. U. S. trademark.

Brometone is made by the action of caustic alkalis on a mixture of bromoform and acetone.

It occurs in fine white, prismatic crystals which possess a camphoraceous odor and taste. It is slightly soluble in water, soluble in alcohol, ether, benzine and most organic solvents. It melts at about 167 C. and volatilizes on exposure to air.

**BROMURAL.**— $(\text{CH}_3\text{CH}(\text{CH}_3)\text{CHBr.CO})\text{HN.CO.NH}_2$ . — 2-monobrom-isovaleryl-urea obtained by the interaction of urea with brom-isovaleryl bromide.

*Actions and Uses.*—Bromural is a nerve sedative which is claimed to produce sleep without markedly affecting the circulation or respiration. All action by bromural is said to cease after from three to five hours. In many cases, however, the sleep caused by the preparation continues beyond the limits of its action. It is claimed to be useful as a nerve sedative and for the purpose of inducing sleep in functional nervous disease. Bromural does not produce the desired effects in cases of insomnia in which pain, cough, angina pectoris or delirium exist.

*Dosage.*—As a nerve sedative 0.3 Gm. (5 grains) three times daily; as a specific at bedtime, 0.6 Gm. (10 grains), which dose may be repeated if advisable during the night, after the action of the first dose has ceased.

Manufactured by Knoll & Co., Ludwigshafen a/Rh., Germany, and New York (E. Bilhuber, New York, distributor). U. S. patent No. 914,518 (March 9, 1909; expires 1926). U. S. trademark No. 61,165. German patent No. 185,962.

*Bromural Tablets, 5 grains.*—Each tablet contains bromural 0.3 Gm. (5 grains).

Bromural forms small, white, almost tasteless needles which are easily soluble in hot water, ether, alcohol and alkalis, but less readily in cold water. It sublimes on heating and melts in the neighborhood of 145 C.

Bromural can be precipitated from a 10 per cent. sodium hydroxide solution with acids. The presence of bromine may be demonstrated with fusion with sodium carbonate and potassium nitrate and testing for a bromide with silver nitrate solution. On heating the alcoholic solution of bromural with sodium ethylate for several hours on the water-bath, sodium bromide will precipitate. If this be filtered off and the filtrate evaporated, a crystalline mass will remain which can

be recrystallized from water. This is dimethylacrylic acid, melting at 280 C. If 1 Gm. bromural be boiled for about one minute with 10 per cent. solution of sodium hydroxide, ammonia obtained from the urea will be given off. If the hot liquid be then cooled, acidified with nitric acid and extracted with ether, and the ether evaporated, an oily fluid, 1-brom-isovaleric acid, which has the specific odor of valeric acid, will remain. The biuret reaction cannot be obtained. On melting bromural and adding concentrated sodium hydroxide solution and copper sulphate, no color reaction will take place.

## CALCIUM SALTS

Calcium performs important functions, especially in the deposition of calcium salts in bone, in the regulation of nervous, muscular and glandular activity, and in the coagulation of the blood.

Rickets and osteomalacia show defective deposition of calcium in the bone, but this seems to be the result and not the cause of the disorder, and cannot be corrected by additional administration of calcium. The normal income of calcium in the food, etc., is ample for the normal needs of the body.

The administration of calcium salts has been shown to decrease the permeability of cells. Accordingly, it lessens all transudation phenomena, and has been found useful against the skin-rashes of serum disease, against other urticarias, against diarrhea, etc. It has probably no effect on more general hydrops, perhaps because it interferes too much with the elimination of water by the excretory channels.

Calcium depresses the nervous functions and is therefore more or less efficacious against convulsions. It cannot usually be introduced safely in effective quantities, but it has recently been asserted that it enhances markedly the sedative effects of bromides in resistant cases of epilepsy (von den Velden: *Therap. Monatsh.*, 27: 685, 1913).

Calcium has been used against hemorrhages, particularly in hemophilia, purpura, typhoid, etc., and to increase the coagulability of the blood in aneurysm. It is, of course, impossible to judge of its efficiency by the clinical course. Determinations of coagulability of the blood have given contradictory results. These seem to be reconciled by the experiments of von den Velden, which showed increased coagulability, but this lasted only half an hour, and is similar to that produced by other salts. It is attributed to the local action on the intestines. Such an effect would be useless therapeutically. Since the calcium is harmless, however, its administration is probably justified.

For oral administration, calcium chloride is generally employed; for hypodermic use, the less irritant lactate is preferred.

**CALCIUM CACODYLATE.**—See Arsenic and Arsenic Compounds (Arsenic Compounds, Complex—Organic—Cacodylates).



**CALCIUM PEROXIDE.**—See Peroxides, Metallic.

**CALCIUM PHENOLSULPHONATE.**—See Phenolsulphonates.

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**CAMIOFEN OINTMENT.**—An ointment obtained by mixing iocamfen (a liquid obtained by the interaction of iodine 10 parts, phenol 20 parts and camphor 70 parts, containing about 7.25 per cent. free iodine) with an equal weight of a mixture composed of lard, wax and oil of theobroma, but containing nearly all of its iodine in the combined form.

*Actions and Uses.*—The ointment has the properties of fatty iodine compounds, phenol and camphor.

It is used in various skin diseases, inflammatory swellings, itching, etc.

*Dosage.*—It is applied directly or on gauze, undiluted or mixed with fatty substances. The parts to which camiofen ointment is applied should be dry and the application of mercuric chloride before or after the use of the ointment must be guarded against.

Prepared by Schering and Glatz, Inc., New York. No U. S. patent or trademark.

**CANTHARIDIN.**—Cantharidinum.— $C_{10}H_{12}O_4$ .—The inner anhydride (lactone) of cantharidic acid.

*Actions and Uses.*—Preparations of cantharidin are used in place of corresponding preparations of cantharides and have the advantage of being more cleanly and more uniform in strength. Cantharidin is recognized by the British, French and Swiss Pharmacopeias. Cantharidin is more toxic to the kidney when the urine is acid than when it is alkaline.

*Dosage.*—From 0.00025 to 0.0005 Gm. ( $\frac{1}{240}$  to  $\frac{1}{120}$  grain).

Cantharidin may be obtained from various species of *Cantharis* or of *Mylabris*. It may be prepared by digesting powdered cantharides with a mixture of concentrated sulphuric acid and acetic ether at ordinary temperature, then mixing with barium carbonate and exhausting the mixture with acetic ether. The solvent may be removed by distillation and the residue allowed then to stand for some time to allow the cantharidin to crystallize. The resulting crystals may be washed with petroleum benzin to remove the fat and then recrystallized from hot alcohol.

Cantharidin occurs as colorless glistening, inodorous crystals; 0.1 Gm. on incineration should leave no weighable residue. Cantharidin is very slightly soluble in water, petroleum benzin or alcohol (90 per cent.); soluble in chloroform (1:65), in acetic ether (1:150), and in acetone (1:40), and is soluble also in fixed oils. A 0.1 per cent. solution in a fixed oil raises blisters when kept in contact with the skin. The melting point is from 210 to 212 C. Cantharidin slowly volatilizes at 100 C., more rapidly at higher temperatures. It is soluble in solution of sodium hydroxide, the solution depositing crystals of cantharidin when acidified. Gently warmed with sulphuric acid it yields a colorless solution, from which it is separated unchanged when freely diluted with water.

**Cantharidin-Merck.**—A nonproprietary brand complying with the standards for cantharidin.

Merck & Co., New York, distributors.

## CHLORAL DERIVATIVES AND SUBSTITUTES

Chloral is still the standard hypnotic of its class; but it presents the disadvantages of being a powerful cardiac and respiratory depressant and of irritating the stomach; also it cannot be used hypodermically. Attempts to modify the drug so as to make it safer have at the same time resulted in weakening its hypnotic action. Attempts to remove its irritant action have been more successful. The following chloral derivatives are described below and include several preparations which are less irritating to the stomach, and at least one which can be given by hypodermic injection (chlorbutanol):

Butyl-chloral hydrate, trichlorbutylidene glycol,  $\text{CH}_3\text{CHCl.CCl}_2\text{CH}(\text{OH})_2$ .

Chlorbutanol (chloretone), 1,1,1-trichlor-2-methyl-propan-2-ol,  $\text{CCl}_3\text{C}(\text{OH})(\text{CH}_3)\text{CH}_3$ .

Chloralformamide (chloralamid)  $\text{CCl}_3\text{CH}(\text{OH})\text{NH.COH}$ .

**BUTYL-CHLORAL HYDRATE.**—Butyl-Chloral Hydratum.—Trichlorbutylidene Glycol.—Croton Chloral Hydrate.—Butyl-Chloral Hydras. —  $\text{CH}_3\text{CHCl.CCl}_2\text{CH}(\text{OH})_2$ . — 2,2,3-trichlorbutan-1, 1-di-ol, a crystalline product obtained by the addition of water to the liquid butyl chloral (2,2,3-trichlorbutanol,  $\text{CH}_3\text{CHClCCl}_2\text{CHO}$ ).

**Actions and Uses.**—The action of this preparation is similar to that of chloral, except that it is said to be less depressing and more analgesic. It has been especially recommended for relief of facial neuralgia.

**Dosage.**—From 0.3 to 1.3 Gm. (5 to 20 grains).

Butyl-chloral hydrate occurs in pearly white, trimetric laminae, having a pungent but not acrid odor, and an acrid, nauseous taste. It fuses at about 77.8 C. to a transparent liquid, which, in cooling, begins to solidify at about 71.1 C. It is soluble in about 50 parts water, and its own weight of glycerin or of alcohol (90 per cent.); it slowly dissolves in 20 parts of chloroform. From a solution in alcohol it is precipitated by the gradual addition of water, in the form of globules said to consist of butyl-chloral alcoholate,  $\text{C}_4\text{H}_5\text{Cl}_3\text{O}$ .  $\text{C}_2\text{H}_5\text{OH}$ . The alcoholic solution is neutral and the aqueous solution neutral or but slightly acid to litmus.

It gives no precipitate with test solution of silver nitrate. It does not yield chloroform when heated with solution of potassium hydroxide or with milk of lime (*chloral hydrate*).

**Butyl-Chloral Hydrate-Merck.**—A nonproprietary brand complying with the standards for butyl-chloral hydrate.

Merck & Co., New York, distributors.

**CHLORALFORMAMIDE.**—Chloralformamidum.—A compound produced by the combination of formamide,  $\text{HCO.NH}_2$ , with chloral,  $\text{CCl}_3\text{CHO}$ . It should be kept in amber colored, well-stoppered vials.

*Actions and Uses.*—Chloralformamide is an analgesic, hypnotic and sedative. It acts much like chloral hydrate but more slowly. Chloralformamide was introduced as tending to depress the heart less than chloral, but this has not been demonstrated to be true of equally effective doses. It is said to be less irritant than chloral in the stomach. Chloral is formed by its decomposition in the body, and is excreted as urochloralic acid, and fatty degeneration has been observed after its prolonged administration.

*Dosage.*—Chloralformamide may be administered dissolved in cold water, or suspended in water with acacia, or in the form of powders which must be dispensed in paraffin or wax paper. Average dose: 1 Gm. (15 grains).

Colorless crystals without odor having a faintly bitter taste. Soluble in 18.7 parts of water and in 1.3 parts of alcohol at 25 C.

It is hydrolyzed by hot water, chloral hydrate and formamide being formed. It melts at 114 to 115 C. and at a higher temperature decomposes.

It is not affected by dilute acids, but alkaline solutions decompose it with separation of chloroform.

If 0.2 Gm. is heated in a dish, no inflammable vapors are given off, and on continued heating no weighable residue should remain.

When 1.0 Gm. is dissolved in 10 Cc. alcohol, the solution does not redden litmus paper. A solution of 1 Gm. formamide in 10 Cc. alcohol does not become turbid at once on addition of silver nitrate solution.

**Chloralamid.**—A name applied to Chloralformamide.

Manufactured by Chemische Fabrik auf Actien, vorm. E. Schering, Berlin, Germany (Lehn & Fink, New York). German patent No. 50,536. U. S. patent Nos. 429,039 and 429,040 (expired).

**CHLORBUTANOL.** — Trichlor-Tertiary-Butylalcohol. — Acetone-Chloroform.— $\text{CCl}_3\text{C(OH).CH}_2\text{CH}_3$ .—1,1,1-trichlor-2-methyl-propan-2-ol, produced by the reaction of acetone on chloroform.

*Actions and Uses.*—Chlorbutanol is said to be absorbed unchanged from the alimentary tract, but to be decomposed in the body. It is a local anesthetic with an action weaker than that of cocaine, but sufficient frequently to prevent vomiting from gastric irritation. Its antiseptic action is said to be fifteen times as strong as that of boric acid. It acts on the central nervous system similarly to chloral, and although the claim has been made that hypnotic doses are without effect on the circulation and respiration independent observers have described a fall of blood pressure and interference with respiration in animals, and consider it fully as dangerous as chloral. In man 100 grains caused severe symptoms, but recovery occurred. It is claimed that no habit is induced,

but this may be because of its restricted employment. It is said to be useful as a mild local anesthetic in dentistry, etc., as a preservative for hypodermic solutions, for insomnia, vomiting, and for spasmodic conditions. It is also said to be useful as an introductory to general anesthesia, as it lessens excitement and nausea.

*Dosage.*—From 0.3 to 1.3 Gm. (5 to 20 grains) dry or in capsules. Hypodermically as a local anesthetic a saturated aqueous solution may be used.

Chlorbutanol is made by the action of caustic alkalies on a mixture of chloroform and acetone. It is a white, crystalline, volatile compound having a camphoraceous odor and taste. It is soluble in water (8:1000), in fixed and volatile oils, and glycerin; very soluble in alcohol, ether, benzine, glacial acetic acid, chloroform and acetone.

**Chloretone.**—A proprietary name applied to chlorbutanol.

Manufactured by Parke, Davis & Co., Detroit. U. S. trademark.

*Actions and Uses.*—An anodyne, antiseptic and emollient solution for use by inhalation as a very fine spray or nebula.

*Chloretone Capsules, 3 grains.*—Each capsule contains chloretone 3 grains.

*Chloretone Capsules, 5 grains.*—Each capsule contains chloretone 5 grains.

*Chloretone Inhalant.*—Chloretone (chlorbutanol), 1 Gm.; camphor, 2.5 Gm.; menthol, 2.5 Gm.; oil of cinnamon, 0.5 Gm.; refined liquid petroleum, 93.5 Gm.

**CHLORINATED EUCALYPTOL.**—Eucalyptol, chlorinated at ordinary (room) temperature.

*Actions and Uses.*—Chlorinated eucalyptol is used as a solvent for dichloramine-T.

*Dosage.*—Solutions of dichloramine-T in chlorinated eucalyptol should preferably be made as required and without the use of heat. If kept in the dark, and contact with water, organic matter and metals be avoided, stock solutions may be used for several weeks. However, if kept for more than a few days, the content of active chlorine should be determined before use.

Eucalyptol is treated with potassium chlorate and strong hydrochloric acid. After standing several hours at room temperature, the eucalyptol is washed, first with water and then with sodium carbonate solution. Dry sodium carbonate is then added to the chlorinated eucalyptol and this allowed to stand for twenty-four hours. The chlorinated eucalyptol is filtered and dried by addition of calcium chloride (J. A. M. A., July 7, 1917).

Chlorinated eucalyptol has the color and odor of eucalyptol.

**Clorinated Eucalyptol (Dakin)-Abbott.**—A brand of chlorinated eucalyptol.



Prepared by the Abbott Laboratories, Chicago. No U. S. patent or trademark.

**Chlorinated Eucalyptol-Squibb.**—A brand of chlorinated eucalyptol.

Prepared by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

**CHLORINATED PARAFFIN OIL-DAKIN.**—Liquid petrolatum, chlorinated at ordinary (room) temperature.

*Actions and Uses.*—Chlorinated paraffin oil-Dakin is used as a diluent for solutions of dichloramine-T, in chlorinated eucalyptol-Dakin.

*Dosage.*—Solutions of dichloramine-T in chlorinated eucalyptol-Dakin and chlorinated paraffin oil-Dakin are unstable, and should not be over four days old. In any instance they should be discarded as soon as a distinct precipitate appears.

Prepared by the Abbott Laboratories, Chicago. No U. S. patent or trademark.

Liquid petrolatum is treated at room temperature with potassium chlorate and strong hydrochloric acid, exposed to bright day light and allowed to stand over night. The chlorinated product is then washed with water, sodium carbonate solution and the oil drawn off, shaken with calcium chloride and charcoal and filtered (J. A. M. A., July 7, 1917).

Chlorinated paraffin oil-Dakin has the general physical properties of liquid petrolatum.

**CITRESIA.**—Magnesium Acid Citrate.— $\text{MgHC}_6\text{H}_5\text{O}_7 \cdot 5\text{H}_2\text{O}$ .—The hydrated acid magnesium salt of citric acid containing not less than 98 per cent. of  $\text{MgHC}_6\text{H}_5\text{O}_7 \cdot 5\text{H}_2\text{O}$ .

*Actions and Uses.*—Citresia has the laxative and purgative action of magnesium citrate.

*Dosage.*—As a laxative 25 Gm. (6 drachms); as a purgative 50 Gm. (1½ ounce). It may be administered by dissolving citresia 25 Gm. in syrup of citric acid 25 Cc. and water enough to make 150 Cc.

Manufactured by Horace North, New York. No U. S. patent or trademark.

Citresia is a white or faintly yellowish-white, crystalline, odorless substance having an acid taste.

Citresia is very soluble in water; insoluble in alcohol, ether or chloroform.

Five Gm. of citresia should dissolve without residue in 25 Cc. of water.

If to 10 Cc. of an aqueous solution of citresia (1 in 20) 1 Cc. of hydrochloric acid and 1 Cc. of sodium phosphate solution be added and the solution be made slightly alkaline with ammonia water, a white, crystalline precipitate should be produced.

If 10 Cc. of the aqueous solution of citresia (1 in 20) be neutralized with potassium hydroxide solution and 1 Cc. of calcium chloride solution added, no precipitate should be produced. After boiling the mixture for one or two minutes, a white, crystalline precipitate should appear.

If 5 Gm. of citresia be shaken with 25 Cc. of alcohol, the mixture filtered, the filtrate evaporated, the residue, if any, dried for one hour at 100 C., and weighed, the weight found should not amount to more than 0.05 Gm. (limit of *citric acid*, and some other impurities).

If from 0.5 Gm. to 0.8 Gm. of citresia be weighed, and the salt dried to constant weight at 75 C., the loss should not amount to more than 30 per cent. (absence of an *undue amount of water*).

If from 0.5 Gm. to 0.8 Gm. of citresia be weighed, the salt ignited and the residue weighed, the ash should amount to not less than 13 per cent.

If from 2 Gm. to 3 Gm. of citresia be weighed, the salt dissolved in 25 Cc. of water and the cold solution titrated with normal potassium hydroxide, using phenolphthalein as indicator, the alkali required should correspond to at least 98 per cent. of hydrated magnesium acid citrate.

1 Cc. of normal potassium hydroxide volumetric solution = 0.30445 Gm. of  $\text{MgHC}_6\text{H}_5\text{O}_7 \cdot 5\text{H}_2\text{O}$ .

If from 0.5 Gm. to 0.8 Gm. of citresia be weighed, the salt dissolved in 50 Cc. of 1 per cent. hydrochloric acid, a slight excess each of sodium phosphate solution and ammonia water added, the mixture allowed to stand 15 hours, the precipitate collected in a weighed Gooch crucible, washed, dried, heated and weighed in the usual way, the weight of magnesium pyrophosphate should correspond to not less than 98 per cent. of hydrated magnesium acid citrate ( $\text{MgHC}_6\text{H}_5\text{O}_7 \cdot 5\text{H}_2\text{O}$ ).

## CODEINE DERIVATIVES

**EUCODIN.**—Methyl-Codeine Bromide.— $\text{C}_{18}\text{H}_{21}\text{O}_8\text{N}(\text{CH}_3)\text{Br}$ .—A brom-methyl derivative of codeine.

*Actions and Uses.*—Eucodin is said to show a marked reduction in toxicity as compared with codeine, and especially diminution of the characteristic convulsive action of codeine. In animal experiments on frogs, rabbits and dogs eucodin showed some diminution in the narcotic action of codeine, while in comparison with codeine the convulsive action was insignificant.

It is said to be useful as a sedative as a substitute for codeine, especially in cough.

*Dosage.*—0.06 Gm. (1 grain). It may be given in solution or in the form of tablets.

Manufactured by J. D. Riedel, Aktiengesellschaft, Berlin, Germany (Riedel & Co., New York). German patent Nos. 166,362 and 175,796. German trademark. No U. S. patent. U. S. trademark No. 88,639.

*Eucodin Tablets.*—Each tablet contains eucodin 0.05 Gm. ( $\frac{1}{2}$  grain).

Eucodin is produced by treating solutions of codeine with methyl sulphate and potassium bromide.

Eucodin is a white powder, melting at 261 C., easily soluble in water, soluble with difficulty in alcohol and insoluble in chloroform and ether. It corresponds to 80 per cent. of codeine and to its own weight of codeine sulphate. It crystallizes in water in large six-sided prisms.

Eucodin is not precipitated from its aqueous solution by the addition of potassium bromide. Eucodin dissolves in concentrated sulphuric acid (1.84) with effervescence and with formation of a light yellow solution (distinction from codeine). When eucodin is warmed with sulphuric acid and a little ferric chloride, a violet-blue color-

tion occurs. With formaldehyde-sulphuric acid, eucodin gives a brown color, which later becomes bluish-black (distinction from codeine). On the addition of potassium hydroxide to an aqueous solution of eucodin, a yellow color but no precipitate is formed. An aqueous solution of eucodin treated with potassium ferricyanide and ferric chloride does not immediately become blue (absence of morphine). On the addition of silver nitrate solution to an aqueous solution of eucodin, a yellowish curdy precipitate of silver bromide, which is gradually reduced to metallic silver, is produced. The addition of ammonia hastens this reduction. Eucodin should not leave a weighable residue on incineration.

## COPPER SALTS

**COPPER CITRATE.**—*Cuprum Citricum.*—Cupric Citrate.  
—The cupric salt of citric acid, containing from 34 to 36 per cent. of copper.

*Actions, Uses and Dosage.*—Copper citrate possesses the astringent and antiseptic properties of other salts of copper somewhat modified by its sparing solubility.

It may be used for the same purposes and in doses similar to those of other salts of copper.

*Copper Citrate Ointment (5 per cent.)*—*M. E. S. Co.*—An ointment containing 5 per cent. of copper citrate and 95 per cent. of white petrolatum, without alcohol or preservative. Manufactured by the Manhattan Eye Salve Co., Owensboro, Ky.

*Copper Citrate Ointment (10 per cent.)*—*M. E. S. Co.*—An ointment containing 10 per cent. of copper citrate and 90 per cent. of white petrolatum, without alcohol or preservative. Manufactured by the Manhattan Eye Salve Co., Owensboro, Ky.

Copper citrate occurs as a green or bluish-green, finely crystalline, odorless powder. It is but slightly soluble in cold water; somewhat more soluble in a cold solution of an alkali citrate, forming a greenish-blue solution; more soluble in a hot solution of an alkali citrate; also soluble in decomposition in ammonia water and in mineral salts.

When dissolved in ammonia water copper citrate yields an intense blue solution. When heated to 90 C. the salt loses water of hydration and assumes a pale blue color. At higher temperature it blackens and at a low red heat leaves a black residue of cupric oxide. If about 1 Gm. of copper citrate be dissolved in 20 Cc. of diluted hydrochloric acid, the solution diluted to 200 Cc. with hot distilled water, the mixture saturated with hydrogen sulphide, filtered, and the filtrate evaporated nearly to dryness on the water-bath, the residue should respond to the usual tests for citric acid. If 0.5 Gm. of copper citrate be dissolved in 10 Cc. of diluted hydrochloric acid and 1 Cc. of barium chloride solution be added no turbidity should at once occur. A solution of 0.5 Gm. of the salt in 10 Cc. of diluted sulphuric acid should not evolve any odor of acetic acid when boiled. The salt should be free from nitrates, chlorides and carbonates. When copper citrate is tested according to the method given in "Reports of the Chemical Laboratory of the American Medical Association," 1910, iii, 29, not less than 34 per cent. of copper should be found.

**Copper Citrate**—*M. C. W.*—A nonproprietary brand complying with the standards for copper citrate.

Manufactured by Mallinckrodt Chemical Works, St. Louis.

**Copper Citrate-Merck.**—A nonproprietary brand complying with the standards for copper citrate.

Merck & Co., New York, distributors.

## COTARNINE SALTS

Cotarnine is an artificial alkaloid derived by oxidation from narcotine, by a process analogous to the derivation of hydrastinine from hydrastine (which again differs from narcotine only by an additional  $\text{OCH}_3$  group). Cotarnine hydrochloride is official in the U. S. P.; the phthalate is marketed as "styptol."

*Actions and Uses.*—Cotarnine is used systematically mainly against uterine hemorrhage; especially in menstrual menorrhagia, endometritis, and congestive conditions. It is ineffective against postpartum hemorrhage or bleeding from gross anatomic lesions; and probably also against hemorrhage in other internal organs. The clinical reports in its favor are often superficial and sometimes contradictory, but seem to justify the preceding statements.

No satisfactory explanation for these actions has been established. The most probable is the (unproven) assumption of a special constrictor action on the uterine vessels. The circulatory changes observed in experiments are small and probably do not occur in the therapeutic use. The uterine stimulation observable on excised uteri, probably does not occur in life.

Local application of cotarnin in substance or concentrated solution has a direct vasoconstricting effect and is used in tooth extraction, epistaxis, etc.

**COTARNINE HYDROCHLORIDE.**—For description see U. S. Pharmacopeia under *Cotarninæ Hydrochloridum*.

*Actions and Uses.*—See general article, *Cotarnine Salts*, above.

*Dosage.*—Internally 0.05 to 0.1 Gm. ( $\frac{1}{4}$  to  $1\frac{1}{2}$  grains) four or five times daily. Because of its intensely bitter taste, it is best given in the form of coated tablets, pills or capsules; or by hypodermic injection (in urgent cases) 2 Cc. of a 10 per cent. solution; externally, as a styptic, pure or in strong solution.

**STYPTOL.**—*Cotarninæ Phthalas.*—Cotarnine Phthalate.— $(\text{C}_{17}\text{H}_{19}\text{O}_3\text{N})_2\text{C}_6\text{H}_4(\text{COOH})_2$ .—The cotarnine salt of phthalic acid.

*Actions and Uses.*—See general article, *Cotarnine Salts*, above.

*Dosage.*—Internally in sugar-coated tablets of  $\frac{1}{4}$  grain each, 3 to 5 tablets a day (up to 9 tablets a day in cases of



dysmenorrhea). Locally as a dusting-powder. By subcutaneous injection (3 grains dissolved in 30 minims of water) for quick arrest of severe hemorrhage.

Manufactured by Knoll & Co., Ludwigshafen a/Rh., Germany, and New York (E. Bilhuber, New York, distributor). U. S. patent No. 742,532 (Oct. 27, 1903; expires 1920). U. S. trademark No. 51,899.

The base cotarnine, obtained from narcotine by oxidation with dilute nitric acid, is combined with phthalic acid to form the neutral salt.

It is a yellow, microcrystalline powder, easily soluble in water. The base is recognized by the tests given under cotarnine hydrochloride.

## CREOSOTE AND GUAIACOL COMPOUNDS

Creosote consists of phenols and phenol derivatives, chiefly guaiacol and cresol. These have essentially similar antiseptic actions, resembling phenol. Creosote and guaiacol are used internally as intestinal and urinary antiseptics (see general article, Naphthol Compounds), as stimulant expectorants in bronchitis and in the treatment of tuberculosis. (Their efficiency in tuberculosis is still debatable.)

Their local irritant actions often interfere with their internal administration. This local action and the toxicity can be minimized, as with other phenols, by masking the active OH group, through replacement of its H by acid radicals, as in the official guaiacol carbonate and in most of the proprietary derivatives. These esters are insoluble and inactive, but, like phenyl salicylate, are saponified in the intestines, liberating their active constituents gradually. These various esters are practically equivalent.

**NOTE.**—The Council wishes it understood that any claims of nontoxicity that are made for drugs that have or are supposed to have important general effects are admitted to this book only when they do not conflict with known facts. In all such instances, however, it is recommended that a claim of lack of toxicity be not accepted too freely but be considered to mean only that toxic effects have not as yet been recognized with the doses that have been studied. The most sincere and apparently justified beliefs concerning this point are often ultimately reversed by extended experience. Much the same may be said regarding any claims that drugs are nonirritating.

**CALCREOSE.**—A mixture containing in loose chemical combination approximately equal weights of creosote and lime.

*Actions and Uses.*—Calcreose, when administered internally, is claimed to have the same actions and uses as creosote. It is claimed that calcreose does not readily produce gastric distress, nausea and vomiting.

There is some evidence to indicate that by the use of calcreose, relatively large quantities of creosote may be administered, but it appears probable that such tolerance is due to the slower absorption and excretion and therefore decreased efficiency. That the creosote contained in calcreose is liberated in the body is evident from the fact that during its elimination by the kidneys it has produced albuminuria and phenol urine.

*Dosage.*—From 0.25 to 1 Gm. (4 to 16 grains) every two to four hours, beginning with small doses and gradually increasing until tolerance is reached. Calcreose may be given in the form of calcreose solution or as tablets (see below).

Manufactured by the Maltbie Chemical Co., Newark, N. J. U. S. patent No. 1,047,961 (Dec. 24, 1912; expires 1929). U. S. trademark No. 94789.

*Solution Calcreose.*—Prepared by adding 454 Gm. (1 pound avoirdupois) calcreose to 3785 Cc. (1 gallon) of water, agitating occasionally during twenty-four hours, filtering and adding enough water through the filter to make 3785 Cc. (1 gallon) of solution.

*Dosage.*—Four to 8 Cc. (2 to 4 fluidrachms) in a half-glass of water, followed immediately by one-half glass of water, beginning with 4 Cc. (1 fluidrachm) in one-fourth glass of water.

*Calcreose Tablets, 4 grains.*—Each coated tablet contains calcreose 4 grains.

According to the patent specifications calcreose is made by the interaction of equal parts of creosote and lime in the presence of water. A minute quantity of phenolphthalein is added to the finished product to improve the color of calcreose solution.

Calcreose is a dark brown powder, having an empyreumatic odor and a sharp phenolic taste. It is partially soluble in water; the alkaline solution containing calcium compounds of the phenolic bodies of creosote while the insoluble portion consists largely of calcium hydroxide and calcium carbonate.

**CREOSOTE CARBONATE.**—For description see U. S. Pharmacopeia under *Creosoti Carbonas*.

**Creosotal.**—A proprietary name applied to creosote carbonate, U. S. P.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent expired.

**Creosote Carbonate-S. & G.**—A brand of creosote carbonate, U. S. P.

Manufactured by Schering & Glatz, Inc., New York.

**Creosote Carbonate-Merck.**—A nonproprietary brand complying with the standards for creosote carbonate.

Merck & Co., New York, distributors.

**GUAIACOL CARBONATE.**—For description see the U. S. Pharmacopeia under *Guaiacolis Carbonas*.

**Guaiacol Carbonate-Merck.**—A brand of guaiacol carbonate, U. S. P.

Merck & Co., New York, distributors.

**Guaiacol Carbonate-S. & G.**—A brand of guaiacol carbonate, U. S. P.

Manufactured by Schering & Glatz, Inc., New York.

**Duotal.**—A proprietary name applied to guaiacol carbonate, U. S. P.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent expired.

**GUAIIAMAR.**—Guaiacolglycerylester.—Glyceryl Guaiacolate.— $\text{CH}_3\text{O.C}_6\text{H}_4\text{O}(\text{CH}_2\text{OH.CHOH.CH}_2\text{), 1:2.$ —The monoguaiacol ester of glycerin.

*Actions and Uses.*—Guaiamar liberates guaiacol, partly in the stomach and partly in the intestinal canal; it is split up by the gastric and intestinal contents, with the assimilation of one molecule of water, into guaiacol and glycerin. By this evolution of guaiacol, guaiamar is believed to exert an antiseptic action in the intestinal canal. It is said not to interfere with the normal process of digestion, but, on the contrary, exerts a tonic action. (See general article, Naphthol Compounds.)

Guaiamar is intended to be used as a substitute for guaiacol in cases in which the latter is indicated. In the form of ointment it has been recommended in acute articular rheumatism.

*Dosage.*—From 0.3 to 1.3 Gm. (5 to 20 grains) in capsules or dissolved in warm water. Locally, in the form of 25 per cent. ointment with wool-fat (lanolin), by itself, or combined with belladonna, zinc or mercurial ointment, etc.

Manufactured by Mallinckrodt Chemical Works, St. Louis. U. S. patent expired.

Guaiamar is prepared by the reaction of 2 molecules of sodium hydroxide, 1 of guaiacol and 2 of monochlorhydrin at from 140 to 150 C. When the alkaline reaction has disappeared, the mass is diluted with water, which leaves the greater part of the glycerin ester undissolved. The portion dissolved in the water solution may be extracted from the latter by ether.

It is a white, crystalline, non-hygroscopic powder, melting at 75 C. and having a bitter, aromatic taste. It is soluble in 20 parts of water at the ordinary temperature, but dissolves best in warm water; it is soluble in alcohol, chloroform, ether and glycerin. Its solutions are neutral to test-paper. It is decomposed by soluble hydroxides and carbonates and by strong acids.

**THIOLCOL-ROCHE.**—Potassium Guaiacol-Sulphonate.— $\text{C}_6\text{H}_3(\text{OH})(\text{OCH}_3)(\text{SO}_3\text{K}), 1:2:6.$ —The potassium salt of orthoguaiacol sulphonic acid,  $\text{C}_6\text{H}_3(\text{OH})(\text{OCH}_3)(\text{SO}_3\text{H}) 1:2:6.$

*Actions and Uses.*—Thiocol-Roche acts as a sedative expectorant. It has the advantage over guaiacol that it is comparatively tasteless, does not disturb digestion and is non-toxic. In thiocol-Roche the guaiacol is so firmly bound that almost none is split off when the salt is administered, and it is a question if its action is due to small quantities of guaiacol set free or to the guaiacol-sulphonic group as a whole.

It is claimed that thiocol-Roche is useful in the treatment of diseases of the respiratory tract, incipient tuberculosis and certain diarrheas.

*Dosage.*—From 0.3 to 1.3 Gm. (5 to 20 grains), dissolved in water or in syrup, or in the form of tablets.

Manufactured by F. Hoffmann-La Roche and Co., Basle, Switzerland (The Hoffman-La Roche Chemical Works, New York). U. S. patent No. 650,218 (expired).

*Syrup Thiocol-Roche.*—A syrup containing thiocol-Roche, 10.5 Gm., in 100 Cc. (6 grains in a fluidrachm).

*Thiocol-Roche Tablets, 5 grains.*—Each tablet contains thiocol-Roche 0.3 Gm. (5 grains).

Thiocol-Roche is prepared by sulphonating guaiacol at a temperature not exceeding 70 to 80 C. with concentrated sulphuric acid, converting the guaiacol sulphonic acid produced into the barium salt, and this by decomposition with potassium sulphate into the potassium guaiacol-sulphonate.

Thiocol-Roche is a colorless, crystalline powder, neutral or faintly alkaline, odorless, and having a faint bitter taste. Thiocol-Roche is soluble in water, slightly soluble in ordinary alcohol, but insoluble in absolute alcohol and in ether or oils.

If to an aqueous solution of thiocol-Roche, barium chloride solution is added, no precipitate is produced; ferric chloride produces an intense violet-blue color, which disappears on the addition of ammonia, or of concentrated solution of alkali chlorides or sulphates.

## CRESOL AND CRESOL PREPARATIONS

Cresols are phenols in which one or several of the hydrogen atoms have been replaced by alkyl groups, especially  $\text{CH}_3$ . This substitution increases the germicidal efficiency, while the toxicity is not increased, at least in the same ratio. The cresols, therefore, possess distinct advantages as disinfectants. In practice, they are much less toxic than phenol, because they are used more diluted, but they are far from being "nonpoisonous." Another advantage of the cresol preparations over phenol is their lower cost. Their disadvantages are the disagreeable odor, which depends mainly on impurities, their limited solubility in water, and their variable composition and activity.

They may be rendered soluble by the addition of soap, as in the official compound solution of cresol and in several other ways. The variability is best discounted by the determination of the phenol coefficient, that is, the ratio of the germicidal power of the disinfectant to the germicidal power



of phenol, tested under identical conditions. (The Council has approved the Hygienic Laboratory phenol coefficient. The details of the test are described in *Hygienic Laboratory Bulletin* 82.) A disinfectant three times as active as phenol would have the coefficient 3 (this being about the coefficient of compound cresol solution). Most disinfectants are now sold with a statement of their coefficient. The degree of dilution for disinfection is obtained simply by multiplying by 50 the phenol coefficient; for instance, a disinfectant having the coefficient 3 would be diluted  $3 \times 50 = 150$  times.

The official cresol and the proprietary trikresol are mixtures of the three isomers of  $C_6H_4.OH.CH_3$ . The "higher homologues," containing two or more methyl groups, have a higher disinfectant coefficient.

**CRESOL**—For description see the U. S. Pharmacopeia under Cresol.

**Cresol-Merck**.—A brand of cresol, U. S. P.

Merck & Co., New York, distributors.

**Purified Three Cresols-Mulford**.—A mixture of isomeric cresols, corresponding closely to cresol, U. S. P.

Manufactured by the H. K. Mulford Co., Philadelphia. No U. S. patent or trademark.

Purified three cresols-Mulford, is soluble in 50 parts of water at 25 C.; it is free from bases, such as pyridine and from hydrocarbons. Its phenol coefficient, determined by the U. S. Hygienic Laboratory method, is not less than 2.5 (the exact value is stated on each package) and of a phenol toxicity, determined by the method of Hale, not greater than 150 per cent. (the exact value is stated on each package).

**DISINFECTANT KRELOS-MULFORD**.—Krelos. — A solution of cresols or higher phenol homologues and rosin soap. It is stated to represent approximately: water, 15 per cent.; sodium oxide, 3 per cent.; pyridin, 1 per cent.; rosin acids, 20 per cent.; phenols, 23 to 25 per cent., and hydrocarbons, 36 to 38 per cent.

*Actions and Uses*.—Mulford disinfectant krelos is an antiseptic, germicide and deodorant.

It is said to be indicated wherever antiseptics or disinfectants are employed.

Manufactured by the H. K. Mulford Co., Philadelphia. No U. S. patent or trademark.

Mulford disinfectant krelos is said to be prepared by addition of coal-tar distillates to a rosin soap solution.

It is a dark-brown, almost black, liquid, having a specific gravity of about 1.066 and a characteristic cresol-like odor. With water it forms an almost white milklike emulsion.

The bactericidal power of Mulford disinfectant krelos is determined by the Hygienic Laboratory method. The phenol coefficient, ranging from 5 to 7, is stated on the label.

**PHENOCO.**—A mixture of coal-tar creosote and higher phenol-homologues, in soap solution. It is stated to contain coal-tar creosote, 8 per cent., phenol-homologues, 62 per cent., and soap 30 per cent.

In the foregoing definition the manufacturers use the term "coal-tar creosote" to signify the product obtained by the destructive distillation of coal, containing 15 per cent. of cresols, but no phenol; while the term "higher phenol-homologues" is used to designate phenols containing two or more methyl groups.

*Actions and Uses.*—Phenoco is an antiseptic and germicide, being in the latter respect from fifteen to sixteen times stronger than phenol. It is stated to be noncaustic, non-irritant and, for mammals, about one-half as toxic as phenol.

It is used in minor surgery, obstetrics, gynecology, ophthalmology, otology, diseases of the skin, etc.

*Dosage.*—Dilutions of from 1 to 5 per cent., or higher, according to the severity of the case.

Manufactured by the West Disinfecting Co., New York. No U. S. patent. U. S. Trademark No. 61,552.

Phenoco is said to be prepared by incorporating a nearly dry, vegetable oil soap with the coal-tar creosote and phenol-homologues at a temperature of 100 C. under continuous agitation until complete solution has taken place.

Phenoco is a dark brown fluid of characteristic, coal-tar-like odor. It is miscible with water in all proportions, forming a white emulsion; it is soluble in alcohol, ether, acetone and in fixed oils, forming clear solutions. It is compatible with physiologic salt solution. It is incompatible with strong alkalis and acids. When tested by the "phenol coefficient" method of the Hygienic Laboratory of the U. S. Public Health Service (*Jour. Infect. Dis.* 8 [Jan.] 1911), it is said to be from fifteen to sixteen times stronger, as a germicide, than pure phenol.

The chemical composition of phenoco is controlled according to the method published in Bulletin 107, Bureau of Animal Industry, "The Analysis of Coal-Tar Creosote and Cresylic Acid Sheep Dips."

## CRESOL DERIVATIVES

The toxicity and local actions of the cresols, as of other phenols, may be diminished by "masking" the active OH group, through replacement of the H by acid radicals.

**CRESATIN.**—Meta-Cresyl Acetate.— $\text{CH}_3\text{C}_6\text{H}_4\text{O}(\text{CH}_3\text{CO})$ .  
—The acetic acid of meta-cresol,  $\text{CH}_3\text{C}_6\text{H}_4\text{OH}$ .

*Actions and Uses.*—Cresatin is said to possess antiseptic and analgesic properties, and is apparently free from toxic effects. It is said to be useful in the treatment of affections of the nose, throat and ear, such as follicular tonsillitis, nasal suppuration due to ethmoid diseases, atrophic nasopharyngeal catarrhs, furunculosis of the external auditory canal and

purulent otitis media. When applied to mucous membranes it is said to cause no irritation, sloughing or discomfort.

*Dosage.*—Cresatin may be employed either in the pure form, or in dilution with oils or alcohol by direct application or spray.

Manufactured by Schieffelin & Co., New York. U. S. patent No. 1,031,971 (July 9, 1912; expires July, 1929). U. S. trademark No. 80,533.

The chemical properties of meta-cresyl acetate were studied by C. Panoff in 1903 (*Jour. Russ. Phys. Chem. Ges.* 35: 93, 1903).

Cresatin occurs as a colorless, oily liquid, possessing a characteristic odor. It is practically insoluble in water, but soluble in the ordinary organic solvents, miscible with liquid petrolatum, fixed and volatile oils and is volatile with steam.

If 10 Cc. cresatin be shaken for one minute with 100 Cc. water and filtered through a wet filter, the filtrate should have a neutral reaction, and should not produce a violet color with ferric chloride solution, or produce a turbidity with silver nitrate solution. If 10 Cc. cresatin be evaporated it should leave after incineration no weighable residue.

**CYPRESS OIL.**—*Oleum Cupressi.*—An oil distilled from the leaves and young branches of *Cupressus sempervirens* L.

*Actions and Uses.*—Cypress oil is said to be useful when administered by inhalation for the relief of whooping-cough.

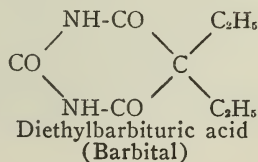
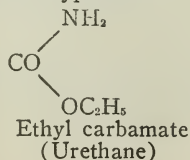
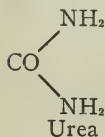
*Dosage.*—The oil should be diluted with 5 parts of alcohol and 15 Cc. (4 fluidrachms) of the mixture sprinkled three or four times daily over the coverlet, pillow and underwear of the child. The application may be repeated once or twice during the night, if recurring attacks are unusually severe.

Cypress oil is a yellowish liquid with a pleasant odor suggesting cypress. After evaporation it leaves an odor that reminds one of laudanum or amber. Its specific gravity is 0.88 to 0.89 at 15 C. and its optical rotation is + 4 to + 18. The oil is soluble in from 2 to 6 parts of 90 per cent. alcohol.

Cypress oil consists chiefly of furfural, d-pinene, d-camphene, cymene, d-sylvestrene, d-terpineol and esters of the same, l-cadinene and cypress camphor.

## DIETHYLBARBITURIC ACID (BARBITAL) AND COMPOUNDS

Barbital (diethylbarbituric acid), which was introduced under the name of "veronal," is chemically related to urea and the carbamate hypnotics:



Phenyl-ethyl-barbituric acid (phenobarbital) is derived from diethylbarbituric acid by replacing one ethyl with phenyl.

*Actions and Uses.*—Diethylbarbituric acid (barbital) is used as a hypnotic in simple insomnia and in the sleeplessness of hysteria, neurasthenia, mental disturbances, and impending delirium tremens. It is more powerful than chloral and somewhat more analgesic; it does not produce local irritation and the taste is not so disagreeable. The margin between the ordinary therapeutic dose (0.5 Gm.) and the toxic dose (usually 8 to 10 Gm.) of barbital is somewhat wider than that of chloral, and the ordinary doses have little effect on the blood pressure and respiration. Fatal collapse (by peripheral paralysis of the blood vessels) has occurred, however, in several cases from relatively small doses (from 10 to 15 grains, 0.65 to 1 Gm.; J. A. M. A., Nov. 27, 1909, p. 1833). Small doses are somewhat diuretic. The action is rather slower than with chloral, but more rapid than with sulphonmethane. After-depression is exceptional, but more common than with chloral. The usual dose (0.5 Gm., 8 grains) induces a deep, dreamless sleep in half an hour, or even more promptly if the soluble sodium salt is used. The patient generally awakens refreshed, but exceptionally suffers from lassitude, vertigo, headache, nausea, diarrhea and skin eruptions.

The excretion is slow, so that ordinary doses may produce cumulative effects resembling those of sulphonmethane, but more slowly. It must therefore be intermitted after a week. The formation of a habit has been reported.

The sodium salt is more soluble than diethylbarbituric acid, but has a bitter alkaline taste.

Phenyl-ethyl-barbituric acid (phenobarbital) is more powerful; but the hypnotic and fatal dose are close together, and the circulatory depression is severe.

**BARBITAL.**—Diethylbarbituric Acid.—*Acidum Diethyl-Barbituricum.*—Diethyl Malonyl Urea.—Malo-Urea.— $\text{CO}(\text{NH}-\text{CO})_2\text{C}(\text{C}_2\text{H}_5)_2$ . Diethylbarbituric acid, 2, 4, 6-trioxy-5-diethyl pyrimidin, a ureide derived from diethylmalonic acid,  $\text{COOH.C}(\text{C}_2\text{H}_5)_2\text{COOH}$ , and urea,  $\text{CO}(\text{NH}_2)_2$ . Barbital was first introduced as veronal.

*Actions and Uses.*—Barbital is quickly absorbed, especially when it is given in solution. In small doses it induces sleep apparently without any other effect. In larger doses the temperature falls and animals show marked trembling and restlessness in their sleep. In small doses it is a relatively safe hypnotic, but fatalities have followed its indiscriminate use.

It is claimed to be useful in simple insomnia, as well as in that accompanying hysteria, neurasthenia and mental disturbances.



*Dosage.*—From 0.3 to 1 Gm. (5 to 15 grains) in hot water, tea or milk, or, if in wafers or capsules, followed by a cupful of some warm liquid.

Barbital may be prepared by the interaction of esters of diethylmalonic acid with urea in the presence of metallic alcoholates. (U. S. patent No. 782,739). It is also obtained by condensation of diethylcyanacetic ester with urea by means of sodium alcoholate.

It is a white, crystalline powder, melting at from 188 to 189 C., odorless and faintly bitter. It is soluble in about 150 parts of cold water and in about 12 parts of boiling water. It is quite soluble in ether, acetone and ethyl acetate; also slightly soluble in chloroform, petroleum benzene, acetic acid and amyl alcohol. It forms salts with alkalis which are soluble in water.

Prolonged heating with sodium carbonate solution liberates ammonia. Deniges' reagent produces a white precipitate; Millon's reagent produces in solution acidulated with nitric acid a precipitate soluble in an excess of the reagent.

**Barbital-Abbott.**—A brand of barbital complying with the N. N. R. standards.

Manufactured by the Abbott Laboratories, Chicago, under U. S. patent No. 782,739 (Feb. 14, 1905; expires 1922) by license of the U. S. Federal Trade Commission.

**Veronal.**—A brand of barbital complying with the N. N. R. standards.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent No. 782,739 (Feb. 14, 1905; expires 1922). U. S. trademark.

*Veronal Tablets, 5 grains.*—Each tablet contains veronal 0.33 Gm. (5 grains).

**BARBITAL SODIUM.**—Sodium Diethyl-Barbiturate.—Sodii Diæthylbarbituras.— $\text{Na}(\text{C}_8\text{H}_{11}\text{O}_3\text{N}_2)$ .—The monosodium salt of barbital (diethylbarbituric acid).

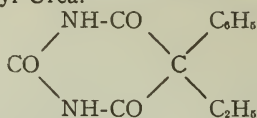
*Actions and Uses.*—The same as those of barbital, but claimed to act more rapidly on account of its greater solubility. Because of its solubility, administration by rectal injection and also subcutaneous injection has been proposed.

*Dosage.*—The same as that of barbital (which see). It should be administered in aqueous solution.

Barbital sodium occurs as a white, crystalline powder, soluble in 5 parts of water at 15 C. and in about 2 parts of oiling water. The aqueous solution of the salt has a bitter alkaline taste.

The salt contains 11.18 per cent. sodium (Na) and should yield about 89 per cent. (theory requires 89.31 per cent.) diethyl-barbituric acid (THE JOURNAL, Jan. 23, 1909, p. 311).

**PHENOBARBITAL.** — Phenyl-Ethyl-Barbituric Acid. — Phenyl-Ethyl-Malonyl-Urea.—



2,4,6-trioxy-5-phenyl-ethyl pyrimidin. Phenyl-ethyl-barbituric acid (phenobarbital) differs from diethylbarbituric acid (barbital) in that one ethyl group ( $\text{C}_2\text{H}_5$ ) has been replaced by one phenyl group ( $\text{C}_6\text{H}_5$ ).

*Actions and Uses.*—It is claimed that the introduction of the phenyl group increases the hypnotic power of phenobarbital (phenyl-ethyl-barbituric acid) over that of barbital (diethylbarbituric acid).

Phenobarbital is said to produce sleep in the cat and dog with a satisfactory range between the effective and lethal doses, affording a deep, quiet sleep, without injury to the respiration or circulation. Very rarely a period of excitement precedes sleep.

It has a sedative action on respiration, lessening the frequency of breathing, although the volume of each respiration is increased. It kills by respiratory paralysis. It is eliminated by the kidneys, a certain portion being probably decomposed in the organism. No renal injuries or gastric disturbances have been observed.

Phenobarbital is claimed to be a useful hypnotic in nervous insomnia and conditions of excitement of the nervous system.

*Dosage.*—From 0.2 to 0.3 Gm. (3 to 5 grains) increased if necessary to 0.8 Gm. (12 grains). A maximum dose of 0.8 Gm. (12 grains) should not be exceeded. Smaller doses are sometimes efficient.

Phenobarbital is a white, odorless, slightly bitter powder. It is almost insoluble in cold water, slightly soluble in hot water and readily soluble in alcohol, ether and chloroform, and in alkaline solutions. It crystallizes from boiling water in lustrous leaflets, and is precipitated unchanged by acids from its alkaline solutions. It melts at from 173 to 174 C.

If about 0.3 Gm. of phenobarbital be shaken for a short time with 1 Cc. of normal sodium hydroxide and 5 Cc. of water, and the mixture filtered, the filtrate will yield white precipitates on the addition of mercuric chloride and of silver nitrate solutions. If about 1 Gm. of phenobarbital be boiled for five minutes in 10 Cc. of a 50 per cent. solution of sodium hydroxide, ammonia will be evolved. If about 1 Gm. of phenobarbital be dissolved in 5 Cc. of normal sodium hydroxide and the solution heated for four hours on a boiling water-bath, the evaporated water being replaced, crystals of phenyl-acetyl-urea will separate on cooling. When recrystallized from dilute alcohol these crystals melt at 147 C. If about 0.1 Gm. of phenobarbital be dissolved in 1 Cc. concentrated sulphuric acid, the solution should be colorless. If about 0.1 Gm. of phenobarbital be incinerated, no weighable residue should remain.

**PHENOBARBITAL SODIUM.**—Sodium Phenyl-Ethyl-Barbiturate.— $\text{Na}(\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3)$ .—The monosodium salt of phenyl-ethyl-barbituric acid.

*Actions and Uses.*—The same as those of phenobarbital.

*Dosage.*—For hypodermic injection phenobarbital sodium is used in the form of 20 per cent. solution, prepared by dissolving the salt in boiled and cooled distilled water; 2 Cc. (30 minims) of the solution contain 0.4 Gm. (6 grains) of phenobarbital sodium. The dose of phenobarbital sodium is 10 per cent. greater than that of phenobarbital.

Phenobarbital sodium may be given hypodermically in doses of 0.1 to 0.3 Gm. ( $1\frac{1}{2}$  to 5 grains).

Phenobarbital sodium is a white, crystalline, hygroscopic powder, readily soluble in water. On long standing or prolonged boiling of the aqueous solution 1 molecule of carbon dioxide is liberated and phenyl-ethyl-acetyl-urea is precipitated. Its aqueous solution is alkaline to litmus.

If phenobarbital sodium be incinerated the residue should respond to tests for sodium. If an aqueous solution of phenobarbital sodium be treated with a solution of potassium pyro-antimonate a white precipitate will be formed. Phenobarbital sodium further responds to the tests given under phenobarbital (which see).

## DIGITALIS PRINCIPLES AND PREPARATIONS

The digitalis group embraces many crude drugs and proximate principles which have a peculiar action on cardiac muscle. Digitalis and strophanthus have been investigated far more than the others, and we are much better informed concerning their actions: from them are derived the active principles and proprietary preparations which have been included in N. N. R.

*Cardiac Action.*—The cardiac action of the individual drugs of the group is very similar and the claims made for the different preparations concern the removal of the disadvantages that have been experienced in the use of the drugs belonging to the digitalis group. The first disadvantage of digitalis medication is the varying strength of the crude drugs. This uncertainty can be avoided by the use of the isolated, definite principles, or to a considerable extent by the use of physiologically standardized preparations. The following methods of standardization are used most extensively:

1. The frog-lethal dose method (M. F. D. in twelve or twenty-four hours).

2. The frog-systolic standstill method, of which there are several modifications.

3. The guinea-pig lethal dose method.

4. The intravenous cat method.

The following biologically standardized preparations of digitalis are described in N. N. R.: digipoten, digitan and digitol. Digitol is a tincture for which freedom from fat is claimed as an advantage. Digipoten and digitan are said to contain the glucosides freed from much of the extraneous matter. The advantage of freedom from fat is not generally considered of importance.

*Differences in Emetic Action.*—The digitalis principles are irritant to certain mucous membranes and the subcutaneous tissues and it has been deduced that the nausea and vomiting which sometimes follow the oral administration of these drugs result from irritation of the gastro-intestinal tract and that these symptoms could be avoided by hypodermic or intravenous use or by the use of certain preparations. It has been shown, however, that digitalis does not markedly irritate the stomach or intestines directly, but that its preparations cause nausea and vomiting almost entirely through their action on the centers in the medulla which are concerned in the production of vomiting. Digitonin and similar substances are present in digitalis in amounts far too small to cause gastric disturbances. It has been shown also that the emetic action is roughly proportional to the cardiac effects of the various members of the group, and when this undesired action is induced it cannot as a rule be avoided by changing the mode of administration, or resorting to other members of the group (see Eggleston, Cary and Hatcher, Robert A.: The Emetic Action of the Digitalis Bodies, J. A. M. A., Feb. 15, 1913, p. 499. Cushny: Am. J. Med. Sc., April, 1911).

*Differences in Absorption.*—Digitalis and preparations representing the entire drug and also digitoxin are absorbed fairly readily from the alimentary tract, and hence their actions may be limited to the therapeutic stage, whereas strophanthus and strophanthin are absorbed more slowly and irregularly with correspondingly greater difficulty in limiting their actions to those desired, when they are administered orally. This disadvantage has been overcome by administering strophanthin intramuscularly or intravenously.

*Differences in Cumulative Action.*—The effects of all the digitalis bodies are said to be cumulative. This cumulative effect is especially pronounced in the case of digitalis itself and digitoxin. It is much less in the case of strophanthus, strophanthin and true digitalin.



## Digitalis Principles

The well-known disadvantages of all the drugs of the digitalis group have served as a constant stimulus in the search for pure principles suitable for subcutaneous and intravenous administration, but despite the numerous investigations directed toward this end the chemistry of digitalis and other members of the group is very imperfectly understood. Several digitalis principles have been isolated in a greater or less degree of purity. Of these, digitoxin and digitalin together represent very nearly the crude drug digitalis. The digitalin on the market, however, is not the true digitalin but the different brands consist of mixtures of two or more principles.

It must be remembered, therefore, that Merck's "crystallized" digitalin, Merck's "pure" digitalin and the "true" digitalin of Boehringer and Soehne, which naturally might be supposed to be identical, differ somewhat in their action.

*Proprietary Digitalis Preparations.*—Several digitalis preparations have been introduced into therapeutic use with the claim that they are composed either of pure principles, or of purified extracts of digitalis, and that they are devoid of certain disadvantages possessed by the preparations of the Pharmacopeia.

It may be said at once that there is no proof that any of these proprietary preparations can be used to greater advantage than digitalis and its galenicals in the majority of cases of cardiac disease. The Council would therefore especially urge on clinicians the necessity of acquiring the necessary skill in the use of the digitalis principles by the careful observation of the actions of a very few of the members of the group, rather than try to use without discrimination of the large number of preparations which are offered. The following principles obtained from the digitalis group are described in New and Nonofficial Remedies: digitalein, crude; digitalin, true; digitalin, "French"; digitalin, "German"; digitoxin; ouabain crystallized, and cymarín.

**DIGITALEIN, CRUDE.**—*Digitaleinum Crudum.*—A mixture of glucosides from digitalis purpurea prepared according to the process of Schmeideberg, containing digitoxin, digitalin and digitalein.

*Actions and Uses.*—Digitalein acts on the heart like digitalis.

Its uses are the same as those of digitalis.

*Dosage.*—From 0.001 to 0.002 Gm. (1/60 to 1/30 grain) two or three times a day.

Commercial digitein is an amorphous, yellowish-white, bitter, powder, soluble in water and absolute alcohol, insoluble in chloroform and ether. The aqueous solution foams on shaking. The solution yields a precipitate on addition of lead acetate, ammonia water or tannic acid.

**DIGITALIN, TRUE.**—*Digitalinum Verum Kiliani.*—Schmeideberg's Digitalin.— $C_{35}H_{30}O_{14}$ .—A glucoside found in the seeds and leaves of *digitalis purpurea* and derived commercially from "German" digitalin.

*Actions and Uses.*—The same as those of *digitalis*. Its action is not so persistent as that of digitoxin. True digitalin is more actively emetic than the other digitalis bodies in proportion to its cardiac activity, and it probably has no advantages over the better known members of the group.

*Dosage.*—It is impossible at present to state the correct dose for digitalinum verum Kiliani. Some authorities have given the same dose as that for digitoxin, whereas others correctly give it as much larger. At least it is quite certain that digitalin is not so active as digitoxin. It is best given in pills made by trituration with sugar of milk and massing with glucose. Aqueous solutions of digitalin rapidly lose their strength and should be freshly prepared.

To a solution of 1 part "German" digitalin in 4 parts of 95 per cent. alcohol, 5 parts of ether by weight (specific gravity 0.720) are added and the mixture allowed to stand in a closed vessel for twenty-four hours. In the clear supernatant solution the quantity of dissolved substance is estimated and the whole then subjected to a vacuum distillation until its weight becomes 1.6 times that of the total dissolved substance. To this concentrated solution water, in an amount 2.4 times the weight of dissolved substance, is added, forming a solution containing approximately 20 per cent. alcohol, from which crude digitalin gradually separates on standing. The crude product is washed first with 10 per cent. alcohol and then with water, and finally dried at a moderate temperature. Further purification is effected by boiling the alcoholic solution with animal charcoal (Kiliani's method, Hager's Handb. der Pharm. Praxis, 1: 1030).

Digitalin occurs as a white amorphous powder, or in characteristic, granular masses. It melts at 217 C. and becomes yellow. It is soluble in 1,000 parts of water and in 100 parts of 50 per cent. alcohol, but nearly insoluble in ether and chloroform. Digitalin dissolved in alcohol and treated with very dilute acid and heat yields digitaligenin and two sugars.

With concentrated sulphuric acid digitalin forms a golden yellow solution which on the addition of potassium hypobromite solution changes to a magnificent rose red or violet red. If a little digitalin is dissolved in 3 to 4 Cc. of glacial acetic acid to which a trace of ferric chloride solution has been added and the mixture carefully overlaid with concentrated sulphuric acid (Keller's reaction) a deep carmine-red band appears; the lower layer of the acetic acid is light yellow, changing to brownish (difference from digitoxin). Sulphuric acid containing a little ferric sulphate gives with a little digitalin at first an intense golden yellow color, and then a red solution; this color rapidly changes to a beautiful and permanent violet. If

too much digitalin is used the red color remains and only the surface layer becomes violet. On heating on platinum foil digitalin should burn without leaving a weighable residue. If a granule of digitalin is covered with 2 Cc. of 10 per cent. potassium hydroxide solution no color should develop within one minute (absence of other glucosides).

If digitalin is stirred to a thin paste with water and for every 100 parts of water used 22 parts of amyl alcohol is added with shaking, and the mixture set aside in a closed vessel for twenty-four hours, the presence of digitonin will be indicated by the formation of distinct masses of crystals.

**DIGITALIN, "FRENCH."**—Homolle's Digitalin.—Digitaline Amorphe.—Digitaline Chloroformique.—A mixture obtained from digitalis purpurea by the method of Homolle, consisting mainly of digitalinum verum Kiliani.

*Actions and Uses.*—Action like that of digitoxin. Uses the same as those of digitalis.

*Dosage.*—What has been said with regard to the dose of digitalinum verum applies to the "French" digitalin; the dose is variously given as from 0.00025 to 0.002 Gm. ( $\frac{1}{240}$  to  $\frac{1}{30}$  grain). Maximum daily dose 0.006 Gm. ( $\frac{1}{40}$  grain). It must be used with caution and its action carefully watched.

One hundred Gm. powdered digitalis leaves are moistened with 1 liter of water and slowly exhausted in a percolator until the percolate amounts to 3 liters. This is precipitated with 250 parts of lead acetate and the filtrate from the precipitate treated with 40 parts of crystallized sodium carbonate and 20 parts of sodium ammonium phosphate, in order to remove the excess of lead. The filtrate is precipitated with 40 parts of tannic acid. The tannate is mixed with 25 parts of powdered litharge and 50 parts of purified animal charcoal and dried. From the dried mass the digitalis bodies are extracted with 90 per cent. alcohol, the latter is distilled off and the residue washed with distilled water and again taken up in 90 per cent. alcohol. This is again distilled and the residue exhausted with chloroform. On expelling the latter the digitalin remains behind (Heger's Pharm. Praxis, 1: 1935).

"French" digitalin is a yellowish-white, amorphous powder of a peculiar aromatic odor and little taste. It is neutral to litmus, almost insoluble in water, soluble in alcohol and chloroform and insoluble in ether. It softens at 90 C. and begins to melt at 100 C. It is not precipitated by solutions of lead salts, but with tannic acid it forms a tannate insoluble in water. Concentrated sulphuric acid dissolves digitalin "French," producing a yellow color, which finally goes over to an emerald-green color.

**DIGITALIN, "GERMAN."**—Digitalinum Germanicum.—A mixture of glucosides obtained from digitalis seeds according to the process of Walz, and consisting largely of digitonin, with digitalin verum and other glucosides.

**NOTE.**—Digitonin is given as a synonym for crystallized digitalin by some manufacturers and it is to be observed particularly that this is quite different from "true digitalin" or the "crystalline digitaline" of the French Pharmacopeia.

*Actions and Uses.*—Similar to those of digitalis.

*Dosage.*—What has been said of the uncertainty of dosage of true digitalin must obviously apply with even greater force to "German" digitalin, since the activity of the latter probably depends mainly on the contained true digitalin. The dose of "German" digitalin was formerly given as 0.001 to 0.002 Gm. ( $\frac{1}{60}$  to  $\frac{1}{30}$  grain) maximum dose 0.004 Gm. ( $\frac{1}{15}$  grain), with a maximum per day of 0.02 Gm. ( $\frac{1}{3}$  grain). Many clinicians, however, have used very much larger doses without ill effects, and the relative activity of certain specimens of the "German" digitalin and other members of the group would seem to indicate that such specimens of "German" digitalin might be given safely in daily doses of a grain or possibly more.

As "German" digitalin (so-called digitalinum purum) is a mixture of very powerful active principles, the proportion of which may vary with changes in the manipulations, it is very important that the directions for its preparation should be very carefully followed, and caution should be exercised to purchase only such products as the manufacturers can guarantee to have been made with the necessary care.

Digitalis seeds are extracted with alcohol, the alcohol driven off, the extract diluted with water and purified by precipitation with lead acetate. The filtrate is freed from lead by sodium phosphate. From the liquid thus purified the digitalis bodies are precipitated with tannic acid, the tannate well washed with water and decomposed with lead or zinc acetate. The digitalin thus separated is taken up in alcohol, the latter carefully distilled off and the residue washed with ether as long as it takes up anything. The digitalin purified in this way is dried at a low temperature and finally powdered. (Hager's *Handbuch der Pharm. Praxis*, 1:1032, 1903).

"German" digitalin is a yellowish-white, amorphous powder, soluble in water and alcohol, insoluble in ether and chloroform. It is said to contain about 50 to 60 per cent. of digitonin and 5 to 6 per cent. of digitalinum verum, the remainder being digitalein and other glucosides.

Sulphuric acid containing a trace of ferric sulphate produces with digitalin, "German," an intense golden-yellow coloration, changing to red and finally to a permanent reddish-violet.

**DIGITOXIN.**—*Digitoxinum.*—*Digitaline Cristallisée* (Native).— $C_{34}H_{54}O_{11}$ .—A glucoside occurring in the leaves of *Digitalis purpurea*. It is the chief active principle of digitalis.

*Actions and Uses.*—Digitoxin acts much like digitalis.

The cardiac action of digitoxin is very persistent, and when the therapeutic effects have passed off, a smaller amount will be required as a rule to reinstate the desired effects than were needed in the first instance. Locally it is extremely irritant; hence it cannot be used for subcutaneous or intramuscular injection. Penzoldt claimed that gastric irritation might be avoided by giving the drug only on a full stomach, but since it has been shown that the nausea and vomiting are almost altogether if not wholly of central origin,



it is difficult to understand how the condition of the stomach contents would influence these disturbances except through a delayed absorption.

**Dosage.**—The toxicity of digitoxin, though very great, has been exaggerated, probably owing to the appearance of symptoms after too frequent repetition of the dose, and the single dose has been given as 0.00025 Gm. ( $\frac{1}{240}$  grain), and a maximum daily dose of 0.001 Gm. ( $\frac{1}{60}$  grain). These doses are undoubtedly too small where it is desired to induce the therapeutic action promptly, though they are approximately accurate where the dosage is to be continued for a time after the therapeutic effects are induced. A sharp distinction should therefore be made between the single or daily dose for *continued use* after the desired effects have been induced, and the dose required at the beginning of treatment.

The beginning single dose is 0.0005 Gm. ( $\frac{1}{200}$  grain); maximum beginning daily dose 0.001 Gm. ( $\frac{1}{60}$  grain). The dose must be reduced, or stopped, immediately when the therapeutic effect or toxic symptoms are induced.

**Antidotes:** Emetics, tannin, nitroglycerin, morphin, alcoholic stimulants or camphor.

Digitoxin occurs in thin, colorless, rectangular, anhydrous leaflets, odorless and having a bitter taste. It is slightly soluble in water, ether and amylic alcohol, easily soluble in alcohol and in chloroform; insoluble in benzin or carbon disulphide; slightly soluble in fatty oils. Digitoxin should not melt below 240 C. If a fragment of digitoxin be dissolved in 2 Cc. of glacial acetic acid containing a trace of ferric chloride and the solution poured on 2 Cc. of concentrated sulphuric acid, a brown color should be produced at the zone of contact of the two liquids. This color gradually changes to green and finally to indigo blue; after half an hour the entire acetic-acid layer will become blue. Digitoxin dissolves in cold, concentrated, hydrochloric acid to a colorless solution, but if this solution be heated on the water bath for some time a green color should be obtained.

Digitoxin dissolves in concentrated sulphuric acid with the production of a green color. If dried at 100 C. digitoxin should not lose more than 1 per cent. of its weight (limit of *adhering moisture*).

**Digitoxin-Merck.**—A non-proprietary brand complying with the standards for digitoxin.

Merck & Co., New York, distributors.

### Related Digitalis Principles

**CYMARIN.**—A neutral, non-glucosidal substance obtained from *Apocynum cannabinum* L. and *Apocynum androsaemifolium* L.

**Actions and Uses.**—Experiments on animals show that cymarin is about equal in activity to the official amorphous strophanthin, which it resembles closely in many of its pharmacologic actions, being far more active after intravenous

or intramuscular injection than after oral administration. Toxic doses cause emesis through the action on the vomiting center in the medulla.

Its uses are much like those of digitalis, but it is not absorbed so readily from the gastro-intestinal tract, at least in animals, and probably in man; hence it is better suited for those cases in which intramuscular or intravenous injection is required to elicit the action promptly. (The usual precautions are necessary.)

*Dosage.*—Single dose for *oral administration* 0.0003 Gm. ( $\frac{1}{200}$  grain); daily 0.001 to 0.002 Gm. ( $\frac{1}{60}$  to  $\frac{1}{30}$  grain). Single or daily dose by intravenous or intramuscular injection, 0.0005 to 0.001 Gm. ( $\frac{1}{120}$  to  $\frac{1}{60}$  grain). Cymarin is sold only in the form of Tablets Cymarin and Ampules Cymarin Solution (see below).

Manufactured by Farbenfabriken, vorm. Friedr. Bayer and Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent No. 1,113,714 (Oct. 13, 1914; expires 1931). German patent No. 255,537. U. S. trademark No. 96,390.

*Tablets Cymarin.*—Each tablet contains cymarin 0.3 mg. (1/200 Grain).

*Ampules Cymarin Solution.*—Each ampule contains cymarin solution representing 0.001 Gm. (1/60 grain) of cymarin.

Cymarin was described by Taub and Fickewirth (*Arch. f. d. ges. Physiol.* 153:239), and according to the German patent (No. 255,537) is prepared by extracting *Apocynum cannabinum* and *Apocynum androsaemifolium*, with organic solvents at a low temperature to prevent decomposition of the active substance, and subsequent recrystallization.

Cymarin occurs as colorless, thick, prismatic crystals possessing a bitter taste. It is only slightly soluble in cold water, more soluble in hot water. It is with difficulty soluble in benzene, ether and carbon disulphide, but dissolves easily in acetone, alcohol and chloroform. When heated it begins to soften at 130 C. and becomes completely liquid at from 135 to 140 C. Cymarin is very sensitive even to weak organic acids, although it is not a glucoside.

If cymarin be dissolved in hydrochloric acid (Sp. Gr. 1.19), a colorless solution results which on standing becomes green and on heating becomes turbid and then yields a resinous precipitate. If cymarin be dissolved in concentrated sulphuric acid a brown solution results. If a trace of cymarin be dissolved in 2 Cc. of glacial acetic acid, to which is added 3 drops of a 1:20 solution of potassium dichromate, a solution will be formed which, when poured on an equal volume of concentrated sulphuric acid, will exhibit at first a brown zone and above that a bright green colored layer. If a trace of cymarin be dissolved in 2 Cc. of glacial acetic acid, to which is added a drop of concentrated ferric chloride solution, a solution will result which, when poured on an equal volume of concentrated sulphuric acid, will develop a dark zone, and then a bluish green line, which gradually colors the acetic acid a deep blue. If a trace of cymarin be dissolved in 10 Cc. of water and 5 Cc. of normal sodium hydroxide solution, a solution will result which when diluted with 1 or 2 drops of a hydrochloric acid solution of diazobenzene chloride or sodium nitrite yields a blue violet color, which on acidifying changes to a brick red. If a trace of cymarin be dissolved in 2 Cc. of glacial acetic acid containing a drop of bromine, a solution will be formed which, after being warmed on the water bath a few minutes, yields a precipitate of white flakes on the addition of double the volume of distilled water.

**OUABAIN, CRYSTALLIZED.**—Crystallized Strophanthin. —G-Strophanthin Thoms.— $C_{30}H_{46}O_{12} + 9H_2O$ .—A glucoside, obtained from *Acocanthera ouabaio* by Arnaud, or, as now commonly prepared, from *Strophanthus gratus*, in which case it is also called crystallized strophanthin, or g-strophanthin Thoms. (The official strophanthin is methyl ouabain [ $C_{31}H_{48}O_{12}$ ].)

**Actions and Uses.**—The pharmacologic action of crystallized ouabain is probably qualitatively identical with that of the official strophanthus or strophanthin, but the crystallized ouabain is more active than the official strophanthin when injected subcutaneously or intravenously. This action develops more rapidly, the drug is more quickly excreted, and shows less tendency to cumulative action than in the case of digitalis.

Crystallized ouabain is used in place of strophanthus or strophanthin as a substitute for digitalis.

**Dosage.**—Ouabain is absorbed so slowly and so irregularly from the alimentary canal that the oral administration of the drug is not to be recommended and is even considered unsafe.

For intravenous or intramuscular administration the dose is 0.0005 Gm. ( $\frac{1}{200}$  grain) and this dose should not be repeated as a rule within less than twenty-four hours. It is best employed dissolved in from 4,000 to 8,000 parts of 0.85 per cent. solution of sodium chloride. When the intramuscular or intravenous dose is to be repeated within less than twenty-four hours a smaller amount should be administered.

Since ouabain solutions may deteriorate rapidly, only recently prepared solutions or solutions which have been recently tested should be used.

**Ouabain Ampules.**—H. W. & D.—One Cc. of solution contains crystallized ouabain, 0.5 mg. Each ampule contains more than 1 Cc. The date of manufacture and an expiration date (three months) is placed on each package. Prepared by Hynson, Westcott & Dunning, Baltimore, Md.

The light-brown deaired seeds of *Strophanthus gratus* are cold pressed to free from oil. The oil-free cakes thus formed are broken up and extracted with 96 per cent. alcohol. The alcohol is distilled off on the water-bath, leaving a residue, which is described as follows: It consists of several layers—an upper thin layer of oil, then an aqueous alcohol layer, followed by a yellowish-brown mass of crystals, under which is a layer of a brown extract, from which an amorphous strophanthin can be isolated. The above-mentioned crystals are freed from the mother liquor and recrystallized from hot water. The seeds yield about 3.62 per cent. of ouabain.

Ouabain forms colorless quadratic crystals of bitter taste and easily soluble in hot water, soluble in 100 parts of cold water and 30 parts cold absolute alcohol and 30 parts amyl alcohol. It is slightly soluble in acetic ether, ether and chloroform. Its solubilities require further study. Solutions of 1 part of ouabain in 100 parts of 95 per cent. alcohol have been frequently observed to deposit crystals on standing.

A solution of 0.01 Gm. in 1 Cc. water run into a layer of concentrated sulphuric acid colors the latter pink to red and the aqueous layer is colored a dirty green color. When crystallized ouabain is

dried at 105 C. it should lose from 18 to 22 per cent. of water and the anhydrous ouabain so obtained should melt at 187 to 188 C. On ignition no weighable residue should remain. Heating with dilute hydrochloric acid or sulphuric acid produces hydrolytic cleavage, yielding a body which is identical with rhamnose.

**Ouabain-Merck (G. Strophanthin).**—A nonproprietary brand complying with the standards for ouabain, crystallized.

Merck & Co., New York, distributors.

## Digitalis Preparations

**DIGIPOTEN.**—A mixture of the digitalis glucosides in soluble form, diluted with milk-sugar to give the preparation an activity approximately equal to that of digitalis of good quality as determined by the U. S. Pharmacopeia. It is standardized by the "one hour frog method." The minimum lethal dose of digipoten per gram body weight of frog is 0.0006 Gm.; or the equivalent in digipoten of 0.0005 mg. of ouabain for each gram of body weight of frog. It contains from 0.3 to 0.4 per cent. of digitoxin as determined by a modified Fromme method; and it is virtually free from digitosaponin (digitonin).

**Actions and Uses.**—Digipoten has the same activity as digitalis leaf of good quality and may be used like the official drug with respect to indications and dosage.

**Dosage.**—The same as that of digitalis.

Manufactured by the Abbott Laboratories, Chicago. No U. S. patent or trademark.

**Digipoten Tablets.**—Each tablet contains digipoten 0.03 Gm. ( $\frac{1}{2}$  grain).

Digipoten is prepared by extracting digitalis leaves with diluted alcohol, the alcohol being removed by distillation *in vacuo*, the resulting extract filtered, and the filtrate precipitated with tannin; the precipitated tannates of the glucosides are washed with water, and the glucosides are liberated in the usual manner. The resulting green brittle powder is triturated with sufficient milk sugar to reduce the activity of the finished product to the standard.

Digipoten is a pale green powder, possessing the characteristic bitter taste of digitalis. It is soluble in water and in 25 per cent. alcohol.

On ignition it leaves no appreciable amount of ash. If 0.1 Gm. of digipoten be dissolved in 2 Cc. of glacial acetic acid containing a trace of ferric chloride and underlaid with concentrated sulphuric acid, there appears at first a brownish zone, changing to red, and finally the upper layer changes to a dark green (digitoxin). In addition to the biological standardization the digitoxin content of digipoten is determined by the following modified Fromme method: 30 Gm. of digipoten are placed in a flask of 500 Cc. capacity, and 270 Gm. of water and 10 Gm. of lead acetate are added and allowed to macerate for three hours with constant agitation. The precipitate is allowed to settle and 207 Gm. of the clear liquid is decanted on a filter of a diameter of 18 Cm. The excess of lead is removed from the filtrate by the addition of 5 Gm. of sodium sulphate dissolved in 6 Gm. of water. The precipitate is allowed to settle and 164 Gm. of the clear fluid, representing 15 Gm. of digipoten, is passed through a filter. This filtrate is transferred to a separatory funnel of a



capacity of 250 Cc. and 4 Cc. of ammonia water is added, after which it is extracted with 4 to 5 portions of 45 Cc. each chloroform, the successive extractions being filtered through a chloroform-wet filter into a tared Erlenmeyer flask. The chloroformic extracts are then evaporated on a water-bath to a constant weight. The crude digitoxin is dissolved in 4 Gm. of chloroform and the solution is poured into a mixture of 10 Gm. of ether and 70 Gm. of petroleum ether with constant agitation. The resulting precipitate is collected on a filter of 5 Cm. diameter and washed with a small amount of petroleum ether. The washed residue is dissolved in hot absolute alcohol and rinsed into the tared Erlenmeyer flask previously used. The alcohol is evaporated on a water-bath and the residue is dried to a constant weight at a temperature of 90 to 100 Cc. and the weight of the purified digitoxin is determined.

**DIGITAN.**—First introduced as *digipuratum*.—A digitalis preparation said to contain digitoxin and digitalin in the form of tannates. It is standardized biologically by the method of Gottlieb. It is claimed that in digitan 85 per cent. of the inactive substances found in the ordinary extract have been removed and that it is free from digitonin.

*Actions and Uses.*—The same as those of digitalis.

*Dosage.*—The same as that of digitalis.

Manufactured by Merck & Co., New York under U. S. patent No. 943,578 (Dec. 14, 1909; expires 1926 by license of the U. S. Federal Trade Commission).

*Digitan Tablets, 1 1/2 grains.*—Each tablet contains digitan 0.1 Gm. (1 1/2 grains).

Digitan is obtained by removing objectionable constituents from an alcoholic extract of digitalis, neutralized with alkaline hydroxides, by the addition of ether, petroleum benzene, or other suitable precipitant, and reducing the purified liquid to a powder, by evaporating with milk-sugar.

Digitan is a greenish-yellow, odorless powder of bitter taste. The active constituents of digitan are insoluble in cold water and diluted acids, but are easily soluble in weak alkalies.

Digitan responds to the following identity test: If 0.1 Gm. digitan is underlaid with about 3 Cc. of glacial acetic acid which contains 1 per cent. of a 5 per cent. solution of ferric sulphate, there appears a red band (presence of digitalin) and above this another, at first bright green, later changing to dark green and finally blue (presence of digitoxin). To determine the digitoxin content, 10 Gm. of digitan are dissolved with moderate heat in 50 Cc. of water; 5 Cc. or 10 per cent. ammonia water are added and the liquid is then extracted with chloroform. The chloroformic extractions are filtered into a tared vessel and the chloroform removed by distillation. The residue is dissolved in 3 Gm. of chloroform and mixed with 7 Gm. of ether and 50 Gm. of petroleum ether. The separated flakes are collected on a small filter. Then the residue on the filter is dissolved in absolute alcohol, allowing the solution to run into the tared distilling vessel. The alcohol is then distilled off and the residue dried to constant weight. The digitoxin thus found should not amount to more than 0.04 Gm.

The physiologic activity is determined by the method of Gottlieb. The activity being adjusted so that the injection into the femoral lymphatic of a freshly caught land frog (*Rana temporaria*) weighing 30 Gm., of 0.2 Cc. of a solution made by treating 1 Gm. of digitan with 19 Cc. of hot water and 1 Cc. of a 2 per cent. solution of sodium bicarbonate causes permanent stoppage of the heart within half an hour in the majority of cases. The part of the activity that is due to digitoxin can be determined by a comparison of the total activity

of the digitan and that of the digitoxin separated in the foregoing quantitative chemical determination. The difference is attributed to digitalin.

**DIGITOL.**—Fat-Free Tincture of Digitalis-Mulford.—A biologically and chemically standardized, fat-free tincture of digitalis, corresponding in drug strength to tincture of digitalis, U. S. P., and containing not more than 70 per cent. alcohol.

*Actions and Uses.*—The same as those of digitalis.

*Dosage.*—0.3 to 1 Cc. (5 to 15 minims).

Manufactured by the H. K. Mulford Co., Philadelphia. No U. S. patent or trademark.

*Vacules Digitol.*—Each vacule contains digitol 30 Cc. in sealed ampules.

The air in the container is removed before sealing, whereby, it is claimed, deterioration of digitol is retarded.

Digitalis which has previously been subjected to percolation with petrolatum benzin is extracted by percolation with the hydro-alcoholic menstruum in the usual way.

It is a brownish-green liquid having a characteristic and highly alcoholic odor and a bitter taste.

It is standardized to contain not less than 0.025 Gm. digitoxin in 100 Cc. and to such a strength that the minimum lethal dose for a 250 Gm. guinea-pig is approximately 1 Cc. Digitoxin may be determined by the method described by Reed and Vanderkleed (*Am. Jour. Pharm.*, March, 1906). The minimum lethal dose on normal (250 Gm.) guinea-pigs is also determined and the preparation adjusted so that 1 Cc. is the minimum lethal dose.

**DIMAZON.**—Diacetylaminooazotoluene. —  $\text{CH}_3\text{C}_6\text{H}_4\text{N:N}.\text{C}_6\text{H}_3(\text{CH}_3)\text{N}(\text{CH}_3\text{CO})_2$ .

*Actions and Uses.*—Dimazon is chemically related to Scarlet R. Like Scarlet R, it stimulates the growth of epithelium, but there are the same differences of opinion as to its clinical value in the treatment of burns, wounds, chronic ulcers, etc. It is claimed that it is less irritating than Scarlet R. It has the advantage that it does not stain the skin, and that it may be removed from linen, etc., by soap and water.

*Dosage.*—Dimazon is generally used in the form of a 2 per cent. ointment made with petrolatum as a base (see below). It is also used dissolved in a fatty oil or mixed with talcum as a dusting powder (see below).

Manufactured by Kalle and Co., Aktiengesellschaft, Biebrich, a/Rh., Germany (Heilkraft Medical Co., Boston, Mass.). U. S. patent applied for. U. S. trademark No. 89,119.

*Dimazon Ointment.*—It is composed of Dimazon 2 parts and petrolatum 98 parts.

Prepared by the Heilkraft Medical Company, Boston.

*Dimazon Oil.*—It is composed of Dimazon 2 parts and olive oil 98 parts.

Prepared by the Heilkraft Medical Company, Boston.

*Dimazon Powder.*—It is composed of Dimazon 5 parts and talcum 95 parts.

Prepared by the Heilkraft Medical Company, Boston.

Dimazon is prepared by the acetylation of amidoazotoluene. It is an orange colored crystalline powder, insoluble in water but readily soluble in alcohol, ether, chloroform, acetone and benzene, oils, fats and petrolatum. It can be removed from cloth by washing with soap and water. It melts at 75 C.

When hydrolyzed with a dilute alcoholic solution of sodium hydroxide, dimazon loses an acetyl group with formation of the insoluble monoacetylamidoazotoluol, which has a melting point of 186 C. Prolonged treatment with an alcoholic alkali solution results in loss of the second acetyl group with formation of amidoazotoluol, melting point 100 C.

Treated with fuming hydrochloric acid, dimazon yields monoacetylazotoluol which is precipitated on dilution with water. Prolonged heating with the acid forms amidoazotoluol and eventually the hydrochloride of the latter.

If dimazon be boiled with alcohol for a long time an acetyl group is removed with formation of ethyl acetate, which may be recognized by its odor.

**DOLOMOL.**—Magnesium stearate,  $Mg(C_{18}H_{35}O_2)_2$ , containing small amounts of magnesium palmitate and oleate.

*Actions, Uses and Dosage.*—Acting as a protective to the skin, dolomol is employed in cutaneous affections as a dusting powder, alone or mixed with various remedies.

The following dolomol compounds are listed: Dolomol-Acetanilid, 25 per cent.; Dolomol-Acid Boric, 20 per cent.; Dolomol-Acid Carbolic, 5 per cent.; Dolomol-Acid Picric, 25 per cent.; Dolomol-Acid Salicylic, 5 per cent.; Dolomol-Acid Salicylic, 10 per cent.; Dolomol-Acid Tannic, 10 per cent.; Dolomol-Alum, 10 per cent.; Dolomol-Aristol, 10 per cent.; Dolomol-Balsam Peru, 10 per cent.; Dolomol-Bismuth Subgallate, 25 per cent.; Dolomol-Calendula, 25 per cent.; Dolomol-Calomel, 25 per cent.; Dolomol-Camphor, 10 per cent.; Dolomol-Guaiacol, 5 per cent.; Dolomol-Iodoform Deodorant, 10 per cent.; Dolomol-Menthol, 5 per cent.; Dolomol-Oil of Cade, 10 per cent.; Dolomol-Resorcin, 10 per cent.; Dolomol-Sulphur Sub., 25 per cent.; Dolomol-Tar, 10 per cent.; Dolomol-Zinc Oxide, 25 per cent.

Manufactured by Pulvula Chemical Co., Jersey City, N. J. No U. S. patent or trademark.

Dolomol is a white powder, insoluble in water, unctuous to the touch, nearly odorless and tasteless. It is claimed to be practically free from oleate. Its magnesium content corresponds to nearly 7 per cent. MgO.

## EPINEPHRINE AND EPINEPHRINE PREPARATIONS

Solutions of the isolated, active principle of the adrenal glands have largely replaced, in practice, solutions prepared from the official *Suprarenalum Siccum*. They have a number of advantages over the latter: they may be made of definite strength, whereas the activity of commercial preparations of the dried glands varies greatly; and they are less liable to bacterial infection. They are, however, much more expensive than solutions made from the dried gland.

Epinephrine may be made synthetically; the preparation originally placed on the market was optically inactive and had only about half the physiologic activity of the natural base. The synthetic product listed below is levorotatory and is in all respects identical with the natural product.

**EPINEPHRINE.**— $C_6H_5(OH)_2(CHOH.CH_2NHCH_3)$ .—1,2-dihydroxy-4<sup>2</sup>-methyl-amino ethyl-4<sup>1</sup>-ol benzene, a substance with feeble basic properties, obtained from the suprarenal gland of the sheep or other animal; also made synthetically.

*Actions and Uses.*—Epinephrine acts peripherally on a variety of structures, probably by stimulating the sympathetic nerve-endings. Its most important therapeutic actions consist in a constriction of the blood-vessels, with consequent high rise of blood pressure; a stimulation of the vague center with slowing of the heart, and a direct stimulant and tonic effect on the heart muscle, similar to digitalis. Large doses also cause glycosuria. Continued administration of large doses to rabbits leads to atheroma. The effect of a single dose is very fleeting. It is not irritant. The effects are seen on local application and intravenous and intramuscular injection. When given to animals, by mouth or hypodermically, moderate doses have almost no action.

Dilute watery solutions rapidly lose their strength, the deterioration being accompanied by a reddish or brownish discoloration.

The alkaloid is chiefly used locally for its vasoconstrictor action, in hemorrhage, and in catarrhal and congestive conditions. It cuts short asthmatic paroxysms (being used by spraying the larynx and by hypodermic injections). Intravenous injections are effective in shock and anesthesia accidents (care being taken not to give an overdose). It has also been recommended in heart disease, Addison's disease, etc., but opinions are divided as to the benefits to be expected from oral administration.

The vasoconstrictor action of epinephrine is used to intensify and prolong the anesthetic effect of local anesthetics by retarding the circulation in the affected part and thus hindering the dilution of the anesthetic agent by too rapid absorption into the general blood-stream.

*Dosage.*—From 0.3 to 2.0 Cc. (5 to 30 minims) of a 1:1,000 solution every two or three hours. Hypodermically, 0.06 to 1 Cc. (1 to 15 minims) of a 1:1,000 solution, diluted with sterile water. Locally it is used in solution varying in strength from 1:15,000 to 1:1,000, for ordinary applications, in oily solution for sprays, in ointment for application to mucous membranes, such as the eye or the nose, where a slower but more lasting action is desired, and in suppositories.



Since the alkaloid is insoluble, solutions in water should be made of some salt, but for the oily solutions the alkaloid itself should be employed.

Epinephrine is a finely crystalline white or yellowish powder, odorless and slightly bitter. It melts at 201 to 207 C., turning brown and decomposing at the higher temperature.

The alkaloid shows a slightly alkaline reaction to moistened red litmus paper. It is almost insoluble in cold water, more readily in hot water. It is soluble with difficulty in alcohol and insoluble in ether. Its solutions are levorotatory. The colorless aqueous solution of the alkaloid is easily oxidized on contact with the air, becoming pink, then red, and eventually brown. The base reacts with acids to form salts which are readily soluble in water; it is also soluble in the fixed alkalies, but not in ammonium hydroxide or in solutions of the alkaline carbonates. The following reactions are the most characteristic: The addition of ferric chloride to a solution of the alkaloid produces a beautiful emerald-green color which by careful addition of caustic alkali becomes purple, and then carmine red. Strong acid prevents the reaction with ferric chloride, limiting the change of color to a dirty yellowish-green. It gives a vivid pink color with iodine. The alkaloid reduces silver salts and gold chloride very energetically, and the liquid turns red. A drop of 1:10,000 solution instilled into the eye will, within a few seconds, produce a pallor of the conjunctiva.

The incompatibilities of epinephrine are the same as those of other alkaloids. Its solutions should be kept tightly stoppered and protected from the light.

**Adrenalin.**—A proprietary name applied to epinephrine.

Manufactured by Parke, Davis & Co., Detroit, Mich. U. S. patent Nos. 730,175, 730,176, 730,196, 730,197, 730,198 (June 2, 1903; expires 1920); 753,177 (Feb. 23, 1904; expires 1921). U. S. trademark.

**Adrenalin Chloride Solution.**—A 1:1,000 solution of adrenalin hydrochloride in physiologic salt solution, preserved by the addition of 0.5 per cent. of chloretone (chlorbutanol).

**Adrenalin Inhalant.**—A neutral oily solution containing adrenalin chloride 1:1,000, 3 per cent. of chloretone, 13 per cent. of alcohol, and aromatics.

**Adrenalin Ointment.**—One part of adrenalin chloride in 1,000 parts of oleaginous ointment base.

**Adrenalin and Chloretone Ointment.**—Contains 0.1 per cent. of adrenalin chloride, and 5 per cent. of chloretone in an ointment base of hydrous wool fat and petrolatum.

**Adrenalin Suppositories.**—One part of adrenalin to 1,000 parts of oil of theobroma (cacao butter). Each suppository weighs about 1 Gm. (15 grains).

**Adrenalin Tablets.**—Each tablet contains 0.001 Gm. (3/200 grain) adrenalin, as borate, yielding a 1:1,000 solution when dissolved in 15 minims (1 Cc.) of water.

**Adrenalin and Cocaine Tablets.**—Each hypodermic tablet contains cocaine hydrochloride 0.01 Gm. (1/6 grain), and adrenalin, as borate, 0.0002 Gm. (1/300 grain).

**L-SUPRARENIN SYNTHETIC BITARTRATE.**—The acid tartrate of synthetic epinephrine obtained by the method of Stolz and Flaecher (*Ztschr. f. physiol. Chem.*, 58: 189).

*Actions, Uses and Dosage.*—See Epinephrine. Synthetic epinephrine has the physiologic effects of natural epinephrine obtained from suprarenal gland.

Manufactured by Farbwerke, vorm. Meister Lucius & Bruening, Hoechst a.M., Germany (H. A. Metz Laboratories, Inc., New York). German patent No. 222,451.

*L-Suprarenin Synthetic Bitartrate Tablets, 0.001 Gm.*—Each tablet contains L-suprarenin synthetic bitartrate, equivalent to 0.001 Gm. (1/65 grain) synthetic epinephrine (free base).

Synthetic epinephrine (the free base) is a white odorless powder nearly insoluble in water, alcohol and ether. It melts at from 211 to 212 C. It rotates polarized light to the left, the rotation being

$$[\alpha] \frac{19.6^\circ}{D} = -51.4^\circ$$

It has the chemical and physical properties of epinephrine obtained from suprarenal glands.

L-suprarenin synthetic bitartrate is a white odorless powder soluble in water yielding a solution which has an acid reaction. L-suprarenin synthetic bitartrate melts at 149 C. and its aqueous solution rotates polarized light to the left.

**PURIFIED EXTRACT OF ADRENAL GLAND-MULFORD.**—An extract of the suprarenal gland, standardized physiologically by measuring its effect on blood-pressure and so adjusted as to correspond to the effect of 4 per cent. of purified epinephrine. It has therefore approximately four times the strength of desiccated suprarenal gland U. S. P.

*Actions and Uses.*—See Epinephrine. Purified extract of adrenal gland-Mulford is not offered for sale, but is used in the manufacture of the preparations listed below and in the appendix.

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

*Adrenal Ointment-Mulford.*—The ointment contains purified extract of adrenal gland, Mulford, 25 parts, and boric acid 1 part, in an ointment base consisting of a mixture of petrolatum and anhydrous lanolin scented with oil of wintergreen and oil of eucalyptus, sufficient to make 1,000 parts.

*Dosage.*—Adrenal ointment is supplied in quarter and half ounce collapsible tubes.

*Urethral Suppositories Adrenal Comp.-Mulford.*—Each suppository contains purified extract of adrenal gland 0.06 Gm. (1 grain), cargentos 0.13 Gm. (2 grains), boroglyceride and gelatine in sufficient quantity.

*Vaginal Suppositories Adrenal Comp.-Mulford.*—Each suppository contains purified extract of adrenal gland 0.06 Gm. (1 grain), cargentos 0.13 Gm. (2 grains), ichthyol 0.13 Gm. (2 grains), with a boroglyceride and gelatine base.

**SUPRARENAL LIQUID.**—Liquor Suprarenalis-P. D. & Co.—An aqueous extract of suprarenal glands, preserved with 0.8 per cent. of chlorbutanol (chloretone). Each Cc.

(16 minims) of the solution represents 1 Gm. (15.4 grains) of the fresh glands.

*Actions and Uses.*—See Epinephrine.

*Dosage.*—The preparation is used undiluted for spraying, especially for mucous membranes.

Prepared by Parke, Davis & Co., Detroit.

**TYRAMINE HYDROCHLORIDE.**—Tyramine. — Parahydroxyphenylethylamine hydrochloride. —  $\text{OH.C}_6\text{H}_4.\text{CH}_2.\text{CH}_2.\text{NH}_2.\text{HCl}$ .—The hydrochloride of the base parahydroxyphenylethylamine  $\text{OH.C}_6\text{H}_4.\text{CH}_2.\text{CH}_2.\text{NH}_2$  obtained synthetically.

*Actions and Uses.*—The actions of tyramine hydrochloride resemble those of epinephrine; they are less powerful but more persistent. It is absorbed much more readily.

Tyramine hydrochloride produces a rise of blood pressure, mainly by vasoconstriction. This suggested its employment in shock or collapse, but it has not been very successful. It is useless as a local hemostatic.

Tyramine hydrochloride seems to have a possible field in obstetrics, since it contracts the uterus and thus checks postpartum hemorrhage; but it is not as powerful as pituitary extract. It is also useful by antagonizing the respiratory depression of morphine, thus rendering this drug safer in childbirth.

*Dosage.*—Tyramine hydrochloride acts fairly well from the stomach, but is best given hypodermically, in doses of 0.02 to 0.04 Gm. ( $\frac{1}{3}$  to  $\frac{2}{3}$  grain), dissolved in water.

The base parahydroxyphenylethylamine was isolated from ergot by Barger and also prepared synthetically by him by the reduction of parahydroxyacetonitrile with sodium in alcoholic solution (Transactions of the Chemical Society, 1909, xcv). It had previously been obtained by heating tryosine; hence its name. It is chemically and physiologically related to epinephrine ( $\text{C}_6\text{H}_3(\text{OH})_2(\text{CHOH}).\text{CH}_2.\text{NHCH}_3$ ).

Tyramine hydrochloride occurs as a white or almost white, crystalline powder, soluble in water and forming a neutral solution.

On careful addition of a few drops of sodium hydroxide solution to a solution of tyramine hydrochloride, a crystalline precipitate of parahydroxyphenylethylamine is produced. Millon's reagent added to a solution of tyramine hydrochloride produces a red precipitate or a red color. If an alkaline solution of tyramine is treated with benzoyl chloride, a dibenzoyl derivative is obtained which melts at 169 C.

A 1:10,000 solution of tyramine hydrochloride produces a distinct contraction in the surviving intestine of the guinea-pig, while doses of 0.001 to 0.005 Gm. produce measurable increase in the blood pressure of the rabbit.

**Tyramine, B. W. & Co.**—A brand complying with the description for tyramine hydrochloride.

Manufactured by Burroughs Wellcome & Co., London, England, and New York. British patent Nos. 1560 and 1561 (Jan. 22, 1909). British trademark No. 309,250. No U. S. patent or trademark.

*Tabloid Tyramine Hypodermic.*—Each tablet contains tyramine, B. W. & Co. 0.02 Gm. ( $\frac{1}{2}$  grain).

**Tyramine-Roche.**—A brand complying with the description of tyramine hydrochloride.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York). No U. S. patent or trademark.

## ERGOT PRINCIPLES AND PREPARATIONS

The confusion as to the active principles of ergot has been considerably cleared. It is now recognized that the older investigators worked with impure mixtures. It has been shown that ergot contains at least two alkaloids and a series of active amines. The numerous names applied to these principles and to impure mixtures render the literature very confusing. The chief constituents are as follows:

1. Ergotoxine or hydroergotinine,  $C_{33}H_{41}O_8N_5$ , an amorphous alkaloid occurring in alcoholic extracts. It is responsible for the characteristic action on the cock's comb and is concerned in the uterine and vascular effects. It is rather unstable and by loss of water changes into its lactone:

2. Ergotinine,  $C_{33}H_{39}O_8N_5$ , a crystalline alkaloid, with very weak actions.

Both alkaloids exist ready formed in ergot, but can be easily converted into each other by chemical means (Barger and Ewins, 1910). Both are insoluble in water and petroleum benzin, sparingly soluble in ether, and readily soluble in most other organic solvents. Ergotoxine is easily soluble in cold alcohol; ergotinine but sparingly. They dissolve in dilute sodium hydroxide, but the ergotinine is partly converted. Their salts form colloidal solutions with water, but these are precipitated by electrolytes (salts or mineral acids).

3. Para-hydroxyphenylethylamine,  $OH.C_6H_4.CH_2.CH_2.NH_2$ . This is closely related to epinephrine in structure and action. It is mainly responsible for the pressor effect, and is not materially concerned in the uterine action.

4. Beta-iminazolyethylamine, 4-meta-aminoethylglyoxaline,  $C_3H_5N_2.CH_2.CH_2.NH_2$ . This lowers the blood-pressure, and stimulates the excised uterus powerfully.

A number of other aromatic amines occur casually, such as agmatine, guanidobutylamine (England and Kutscher, 1910), which has a weak stimulant action on the excised uterus, isoamylamine, etc. Acetyl-choline is frequently present, and lowers the blood-pressure by a cardiac action.



The aromatic amines are also produced in the putrefaction of meat and in the intestinal tract, and have been prepared synthetically. They are derived from the amino-acids by the elimination of carbon dioxide; para-hydroxy-phenyl-ethylamine from tyrosine; beta-iminazoly-ethylamine from histidine; agmatine from arginine; isoamylamine from leucine.

Ergotine is a name applied to a variety of pharmaceutical extracts, generally prepared in such a way that they must contain mainly the amines, and relatively little of the alkaloids.

It will be seen that several of the constituents exert uterine actions, and it is not yet known which of these is the most important in the effects of the crude drug. The galenic preparations must vary in composition according to the solvent. The alcoholic fluidextract probably owes its activity mainly to ergotoxine; the aqueous preparations, including the solid extracts and "ergotines," owe theirs probably to the amines, particularly to histamine. The isolated principles have not been used sufficiently to decide whether or not they can take the place of the natural mixture.

All ergot preparations, especially those containing water, deteriorate with age. It would therefore be of advantage to standardize the ergot preparations. Because of the complex composition, no satisfactory chemical assay has been devised. Different methods of bio-assay have been proposed; but because of the multiplicity of the actions, it is not certain how perfectly these tests reflect the therapeutic efficiency of the drug. The cock's comb method is the most widely employed. It has at least a negative value, for samples which do not respond to this test may be considered worthless.

The following preparations are included in New and Nonofficial Remedies:

Isolated principles: ergotinine citrate; tyramine hydrochloride; histamine hydrochloride (not used in medicine).

Liquid extracts: cornutol; secacornin.

Solid extracts, purified: extract of ergot, purified.

**CORNUTOL.**—*Liquid-Extractum Ergotæ*—Mulford. — A biologically tested liquid extract of ergot, containing the water-soluble, alcohol-insoluble, constituents of ergot and about 10 per cent. alcohol.

*Actions and Uses.*—Cornutol has the actions and uses of ergot.

*Dosage.*—Hypodermically, from 0.65 to 2 Cc. (10 to 30 minims) by the mouth, from 0.65 to 4 Cc. (10 to 60 minims) repeated as often as may be necessary. On account of the deterioration liable to occur in this preparation, the date when it was tested appears on each package.

Manufactured by H. K. Mulford Co., Philadelphia. No U. S. patent. U. S. trademark No. 50,043.

*Ampuls Cornutul.*—Each ampule contains cornutul 2 Cc. (30 minims).

*Vacules Cornutul.*—Each vacule contains cornutul 30 Cc. (1 fluid-ounce) in sealed ampules. The air in the container is removed before sealing, whereby, it is claimed, deterioration of cornutul is retarded.

Cornutul is made by removing fat from ergot with petroleum benzine, percolating the fat-free drug with water, purifying with strong alcohol and concentrating *in vacuo*;  $2\frac{1}{2}$  parts of drug are employed in the manufacture of 1 part of cornutul.

It is a brownish-red liquid, having a characteristic, not unpleasant, odor and disagreeable taste.

When 0.04 Cc. cornutul per kilo weight of animal is injected intravenously into dogs, a rise in blood-pressure of not less than 12 mm. is produced.

**ERGOTININE CITRATE.**—*Ergotinina Citras.*—The citrate of ergotinine, a crystalline alkaloid, probably  $C_{36}H_{39}O_6N_3$  (Barger and Carr), derived from ergot.

*Actions and Uses.*—According to the investigations of Barger and Dale, ergotinine has very slight physiologic activity when it enters the system unchanged, but it is liable to be converted to a certain extent into ergotoxine which possesses marked physiologic activity and appears to represent the pharmacologic actions of ergot. The action of ergotinine, when given by mouth or when injected hypodermically, is variable in intensity but represents the action of ergot.

Ergotinine citrate can be used as a substitute for ergot, and is said to act efficiently, when injected hypodermically, in the treatment of headaches and uterine hemorrhage.

*Dosage.*—From 0.00032 to 0.00064 Gm. ( $\frac{1}{200}$  to  $\frac{1}{100}$  grain) hypodermically.

Ergotinine is obtained by extracting the residue left on evaporation of an alcoholic tincture of ergot with light petroleum to remove oily matter, dissolving the residue in ethyl acetate and shaking with citric acid solution. Sodium bromide or hydrobromic acid is then added and the precipitated hydrobromides of the alkaloids, ergotinine and ergotoxine are collected. The mixed hydrobromides are dissolved in caustic soda and shaken with ether; in this way ergotinine is removed first. Finally, the ergotinine is crystallized from alcohol, leaving ergotoxine and impurities in the mother liquor. By interaction of ergotinine with citric acid, ergotinine citrate is obtained.

Ergotinine citrate is a grayish-white, amorphous powder, slowly soluble in water; it has an acid reaction to litmus paper. Ergotinine crystallizes in long needles, the sides of which are not quite parallel, which darken and melt at temperatures from 219 to 229 C. One part of ergotinine dissolves at 18 C. in 292 parts of alcohol, 1,020 parts of absolute ether, in 91 parts of ethyl acetate, and is moderately soluble in acetone and benzene, and readily soluble in chloroform. It is insoluble in light petroleum and in water. Its specific rotation in alcoholic solution saturated in the cold is  $+338^\circ$ . It forms salts which produce colloidal solutions in water which are precipitated by electrolytes so that they are little soluble in the presence of the stronger mineral acids.

Tests: Ergotinine citrate, when carefully decomposed by alkali, the mixture extracted with ether and the ether evaporated, yields a residue which responds to the test for ergotinine. Solutions of ergotinine have a bluish violet fluorescence, especially when acidified. Concentrated sulphuric acid colors the alkaloid at first yellow, after some hours violet and at length blue. If a small quantity of ergotinine is dissolved in concentrated sulphuric acid and a trace of ferric chloride added, the mixture takes on an orange red coloration, which soon passes into red, while the edges of the liquid are colored blue or bluish green. If a few milligrams of ergotinine are dissolved in about 4 Cc. of glacial acetic acid, a trace of ferric chloride added and the mixture underlaid with concentrated sulphuric acid, a beautiful violet color appears at the junction of the two liquids.

**Ergotinine Citrate-B. W. & Co.**—A nonproprietary brand complying with the standards for ergotinine citrate.

Manufactured by Burroughs Wellcome & Co., London, England, and New York. No U. S. patent or trademark.

**Tabloid Ergotinine Citrate.**—Each tablet contains ergotinine citrate 0.00032 Gm. ( $\frac{1}{200}$  grain).

**Ergotinine Citrate-Roche.**—A non-proprietary brand complying with the standards for ergotinine citrate.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (The Hoffman-LaRoche Chemical Works, New York).

**EXTRACT OF ERGOT, PURIFIED.**—*Extractum Ergotæ Purificatum.*—*Ergotin Bonjean.*—*Extractum Secalis Cornuti.*—*Extractum Ergoti.*—An aqueous extract of ergot purified by alcohol.

**Actions and Uses.**—Purified extract of ergot has the action and uses of ergot.

**Dosage.**—From 0.2 to 0.5 Gm. (3 to 8 grains).

This preparation should not be confused with the following:

**Ergotin Wernich (Pure Dried),** a purified and dialyzed dried aqueous extract of ergot.

**Ergotin Wernich (Liquid),** a dialyzed extract of ergot, in the form of a reddish-brown liquid.

**Ergotin Wernich (Soft),** a purified and dialyzed soft extract of ergot; a reddish-brown syrupy liquid.

**Ergotin Wiggers (Pure Dried),** a dried, alcohol-purified extract of ergot.

**Ergotin Yvon,** a fluidextract of ergot prepared by extracting with dilute solution of tartaric acid.

Powdered ergot is extracted by percolation with water and the percolate concentrated, diluted with alcohol, allowed to stand, then filtered and the filtrate evaporated to a soft extract.

It is reddish-brown, of characteristic odor and taste, soluble in water and in a mixture of equal parts of water and alcohol. The aqueous solution is yellowish-brown and acid in reaction.

If 2 Cc. of an aqueous solution (1:20) is mixed with 7 Cc. of water and 1 Cc. Mayer's reagent, there should appear at most but slight turbidity; the turbidity is increased by the addition of a trace of hydrochloric acid; the further addition of 5 drops of dilute acid produces within a few minutes a flocculent precipitate. 10 Cc. of a 1:20 solution of purified extract of ergot should become turbid on the addition of 1 Cc. picric acid solution and precipitation should occur within five minutes. If a solution of 0.2 Gm. purified extract of ergot in 5 Cc. water is made alkaline with 1 to 2 drops of ammonia water and then shaken out with ether, the ether extract evaporated and the residue dissolved in 2 Cc. acetic acid to which a trace of ferric chloride has been added and the mixture carefully poured on concentrated sulphuric acid, a bluish-violet color appears at the zone of contact.

**Ergotin-Merck.**—A nonproprietary brand complying with the standards for extract of ergot, purified.

Merck & Co., New York, distributors.

#### HISTAMINE HYDROCHLORIDE.—

$$\begin{array}{c} \text{C} \text{---} \text{H} \\ | \quad | \\ \text{H N} \quad \text{N} \\ | \quad | \\ \text{H C} \text{=} \text{C} \text{---} \text{CH}_2\text{CH}_2\text{NH}_2\text{HCl.} \end{array}$$
 — The hydrochloride of the base beta-iminazolyethylamine (histamine). Histamine is closely related to histidine, from which it differs in that one molecule of carbon dioxide has been eliminated.

**Actions and Uses.**—Histamine hydrochloride has a powerful contractile action on certain muscular fibers and a strong vasoconstrictor action. The available evidence does not warrant a recommendation for its therapeutic use, but it is a valuable reagent for the standardization of pituitary and similar preparations.

Histamine was first prepared synthetically from iminazolypropionic acid by Windaus and Vogt in 1907 (*Berl. d. deutsch. chem. Gesellsch.*, **40**: 3691, 1907); it was then prepared by bacterial putrefaction of histidine in 1910 by Ackermann (*Ztschr. physiol. Chem.*, **10**: 504, 1910) and isolated from ergot in 1910 simultaneously by Kutscher (*Zentralbl. f. Physiol.*, **24**: 163) and Barger and Dale (*Pharm. Jour.*, June 4, 1910, p. 710; June 18, 1911, p. 757).

Histamine hydrochloride melts at 240 C. (Corr.).

When picric acid is added to an aqueous 1 per cent. solution of histamine hydrochloride, histamine picrate is precipitated promptly; the precipitate should melt at 234 C. (Corr.). Any impurity present in the histamine hydrochloride will prevent or at least very much retard the precipitation of this picrate.

If a 1:1,000 solution of histamine hydrochloride is made alkaline with sodium hydroxide and a solution of diazobenzosulphonic acid (Pauly's reagent) made alkaline with sodium hydroxide be added, a cherry red color appears.

If a 1:1,000 solution of histamine hydrochloride is mixed with an excess of bromine water, then boiled until the bromine is evaporated and sodium hydroxide added to the solution, a black discoloration occurs.



**Imido-Roche.**—A name applied to histamine hydrochloride.

Manufactured by F. Hoffmann-LaRoche and Co., Basle, Switzerland (Hoffmann-LaRoche Chemical Works, New York). No U. S. patent or trademark.

*Ampules Imido-Roche.*—Each ampule contains 1.1 Cc. of an aqueous 1:1,000 solution of imido-Roche (1 Cc. contains 1 mg.).

**SECACORNIN.**—**Ergotin-Roche.**—A solution of the active principles of ergot in a menstruum consisting of distilled water, glycerin and 7.5 per cent. of alcohol. One Cc. of secacornin corresponds to 4 Gm. of ergot U. S. P. and is said to be standardized according to the method of Kehrer (*Arch. f. exper. Path. u. Pharmacol.*, 58).

*Actions and Uses.*—The same as those of ergot.

*Dosage.*—0.5 Cc. (8 minims) are equivalent to 2 Cc. (30 minims) of fluid extract of ergot U. S. P. It may be given by intramuscular injection in doses of from 0.5 to 1 Cc. (8 to 15 minims).

Manufactured by F. Hoffmann-LaRoche and Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York). No U. S. patent. U. S. trademark No. 58,830.

Secacornin is prepared from ergot by removing fat by means of benzin or similar solvent and exhausting by percolation with diluted alcohol. The total percolate is then deprived of its alcohol by distillation *in vacuo*. The resinous mass which separates after cooling is then carefully drained off and the clear filtrate, having been evaporated to the consistency of an extract, is mixed with the general vehicle.

Secacornin is a dark brown solution, said to be sterile. It is claimed that it does not deteriorate on keeping.

Secacornin responds to the following identity test: 1.6 Cc. secacornin is mixed with 3 Cc. distilled water and 5 drops of 10 per cent. ammonia water and shaken out in a separatory funnel with 20 Cc. of ether. After complete separation of the two liquids the aqueous solution is allowed to flow off, the remaining ether washed with 2 Cc. distilled water and the wash-water likewise carefully separated. After this the ethereal solution is filtered into an Erlenmeyer flask and traces of water removed by the use of as much anhydrous sodium sulphate as can be held on the point of a knife. Following this it is filtered into a small glass dish and cautiously evaporated. The residue is then dissolved in from 1 to 1.5 Cc. ferric-chloride-acetic acid (1 drop of Liq. ferri chloridi with 200 Cc. acetic acid). To this solution is added with a pipette, cautiously and without mixing, in order to form an understratum, 3 Cc. pure concentrated sulphuric acid. At the point of contact of the two liquids a characteristic blue to violet ring forms after a time.

**TYRAMINE HYDROCHLORIDE.**—See Epinephrine and Epinephrine Preparations.

## ETHYLENE AMINES AND DERIVATIVES

Several derivatives of ethylene diamine or 1, 2-diamino ethane,  $\text{H}_2\text{N}.\text{CH}_2.\text{CH}_2.\text{NH}_2$  are used in medicine.

A more complex product, diethylene diamine, piperazine, may be looked on as a condensation derivative of the first and may be obtained from it in small amount by direct heating of its hydrochloride. From this substance a considerable number of derivatives have been obtained, several of which have been introduced into medicine.

The medical applications of these two drugs in medicine depend on their solvent action on tissues and certain products of metabolism. They both form solutions in water which are strongly alkaline without being very caustic or corrosive.

Ethylene diamine is a constituent of argentamin, a solution containing 10 per cent. of silver nitrate. The ethylene diamine is claimed to render the silver salt less irritant and more penetrating.

### Ethylene Diamine Preparations

**ETHYLENE DIAMINE.**—Æthylendiamin. — Æthylene Diamine. — Ethane Diamine. — *a. b.* Diamino-Ethane. —  $\text{CH}_2(\text{NH}_2).\text{CH}_2(\text{NH}_2)$ .—1,2-diamino-ethane.

*Actions and Uses.*—Ethylene diamine is said to be non-corrosive and useful as an albumin solvent for the solution of false membranes in diphtheria and similar affections of the mucous membranes. It is presented for use in the form of kresamine (which see).

Ethylene diamine is prepared by heating 1,2-dibrom-ethane, ethylene bromide, with an excess of alcoholic ammonia, for twelve hours at 100 C., removing the ammonium bromide formed by filtration, evaporating the filtrate to dryness, distilling the residue with potassium hydroxide, and collecting the fraction distilling between 115 and 130 C. and bringing the liquid by successive purifications to constant boiling-point at 117 C.

It is a clear, colorless, thick liquid, having a specific gravity of 0.87, boiling at 117 C., without decomposition, having a strong alkaline reaction, an ammoniacal odor and a caustic taste. It is freely soluble in water and may be mixed with cresols, but is not miscible with benzene (benzol) or ether. It dissolves albumin, even when boiled, very readily.

Since it is a strong base, its incompatibilities are about the same as those of sodium hydroxide.

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**FERMENTDIAGNOSTICUM.**—Solution of Glycyltryptophan-Kalle.—A specially prepared solution of glycyltryptophan for use in determining the presence of a peptolytic ferment.

*Actions and Uses.*—Glycyltryptophan is decomposed in the presence of certain ferments into tryptophan and glycine (amino-acetic acid). The presence of tryptophan is determined by the characteristic test for that substance. If tryptophan is found in the solution after incubation with a suspected solution (stomach contents) it is concluded that a peptolytic ferment was present in the substance tested.

As peptolytic ferments are not present in stomach contents except after regurgitation from the intestine or in the presence of cancer, it is claimed that fermentdiagnosticum may be applied as a test for the diagnosis of cancer in the stomach. Since, however, it appears that the saliva of some individuals contains a ferment capable of splitting glycyltryptophan and since, according to some, the ferments of a gastric carcinoma are not found in the gastric contents unless the tumor is undergoing ulceration, the test has a number of limitations which diminish its value.

*Dosage.*—Each bottle contains a quantity sufficient for one reaction, the solution being covered with toluene for preservation. The material to be tested should be examined for bile and blood and tested with bromine water or bromine fumes for the presence of tryptophan. If these tests give negative results the stomach fluid is suitable for the application of the fermentdiagnosticum.

The bottle is filled to the mark with filtered stomach contents and placed in the incubator for twenty-four hours. It is then taken out and from 2 to 3 Cc. of the solution underneath the toluene layer are removed and tested for the presence of tryptophan.

Manufactured by Kalle & Co., Biebrich a/Rh., Germany (Kalle Color & Chemical Co., Inc., New York). German trademark. No U. S. patent or trademark.

## FERMENTS, DIGESTIVE

The digestive ferment preparations described in New and Nonofficial Remedies represent efforts to produce preparations specially adapted to specific purposes, or preparations of a digestive activity superior to the official preparations.

In medicine digestive ferments or enzymes are used internally for the purpose of supplementing or replacing deficient or absent normal secretions; outside the body for the digestion of food prior to its administration, and locally for the softening of dead tissues or the solution of false membranes. The utility or need for the internal administration of ferments is problematical. When ferments are administered the physician should be assured of their activity and should administer them in a way most likely to secure the desired action of the ferment. To permit a systematic consideration the digestive ferments described in New and Nonofficial Remedies are classified, according to their prominent mode

of action, as amylolytic, proteolytic (including enzymes of the type of pepsin and rennin, trypsin and erepsin), lipolytic, or mixtures exhibiting more than one distinctive enzymatic activity.

Most digestive ferment preparations used in medicine are prepared from the digestive glands. The *peptic ferments* digest proteins and curdle milk under appropriate conditions. They are much used for coagulating milk in the preparations of junket, whey, etc. They are also used to favor the digestion of proteins in the stomach. For this purpose they act efficiently only in the presence of hydrochloric or some similar acid. The occurrence of free hydrochloric acid in the stomach contents indicates the presence of a sufficient amount of pepsin to digest protein food. In such cases the administration of pepsin or any of its preparations is superfluous. If an insufficient amount of hydrochloric acid is found in the stomach contents, pepsin may still be present in sufficient quantity.

*Determination of Peptic Value.*—1. Proteolytic Power in Acid Mediums (for pepsin and gastric preparations): This is determined by the U. S. P. method.

2. Milk-Curdling Power (for rennet and gastric preparations): The method is based on the quantity required to coagulate 100 Cc. of milk. Time limit, temperature and other conditions should be stated.

The *tryptic ferments* are commonly prepared from pancreatic tissue. Dried pancreas and pancreatic extracts are generally supposed to contain all the ferments characteristic of the gland. They are extremely uncertain in their activity, however. The starch-digesting action (amylase or diastase content) is generally the most satisfactory, although it varies greatly. The protein digestion (trypsin content) is so slight, with many samples, as to be practically negligible, and the fat-digesting lipase or steapsin, because of its instability, is practically absent from all. Most pancreatic preparations are very unstable, even when undiluted, and after dilution, they often deteriorate within a day (Long and Muhleman: *The Mutual Action of Certain Digestive Ferments*, *Arch. Int. Med.*, 13:314 [Feb.] 1914). The so-called isolated ferments are more or less purified extracts.

*Trypsin* acts in a slightly alkaline medium on proteins and nucleoproteins, converting them into peptones and polypeptids, and carries the splitting so far as to break these down into the amino-acids. It acts best at a temperature of 40 C. and in a feebly alkaline medium not exceeding a strength of 1 per cent. of sodium bicarbonate. Trypsin is largely destroyed in the stomach and there is very little reason to expect any action from it in the intestines when it is given by the mouth.

Trypsin is used for the partial digestion of food outside the body. It has been said to be useful in malignant tumors when injected into the tumor mass. The claims made in



favor of this method have not been generally accepted and it is not without danger. Trypsin has been applied locally for the solution of diphtheric and other false membranes.

In aqueous solution the enzyme is labile, and aqueous solutions for assay or for any application of the enzymes are to be prepared only at the moment required. It should not be kept for any length of time in any solution of an alkaline or acid reaction or it will be decomposed. It is more readily soluble in alcohol of 25 to 50 per cent. strength and in such menstruum is relatively stable. It is most stable in 50 per cent. glycerol.

Trypsin, in any menstruum in which this enzyme is stable, exerts (in *vit.*) a destructive influence on other enzymes, whether those normally associated with trypsin—amyllopsin, for instance—or placed in contact with it in solution, as, for instance, pepsin.

*Determination of Tryptic Value.*—The U. S. P. method for the valuation of tryptic energy of pancreatin is a crude one and not practically valuable. A much better method is the Fuld-Gross method, which is definite and easily carried out.

It depends on the digestion of a sodium caseinate solution to the point at which it no longer gives a precipitate with dilute acetic acid. A casein solution of 0.2 per cent. strength is prepared by dissolving 100 mg. of pure casein in 2 Cc. of twentieth-normal sodium hydroxide, by aid of very gentle heat, and diluting to 50 Cc. A dilute acid is prepared with 50 Cc. of alcohol, 49 Cc. of water and 1 Cc. of 100 per cent. acetic acid.

The trypsin solution is made by dissolving in the proportion of 20 mg. to 50 Cc. of water.

Six portions of the casein solution of 5 Cc., each containing 10 mg. of casein, are measured out, and diminishing portions of the ferment solution are transferred to test-tubes, but always made up to 5 Cc. For the milligram of casein the weights of ferment may be taken as follows: 2 mg., 1.3 mg., 0.8 mg., 0.5 mg., 0.3 mg., and 0.1 mg. The series of test-tubes containing casein and ferment so charged are incubated one hour at 40 C. and then withdrawn from the bath. To each tube 3 drops of the dilute acetic acid are added. If full digestion has taken place the acid fails to produce a precipitate. The last tube in which no precipitate is formed gives an approximate measure of the digesting power of the ferment, which may be sufficient.

A closer result may be obtained by making up a new series of ferment solutions of just one-tenth the strength of the last. These are to be incubated with the casein solution in the same way, the final tests being made as before.

When tested in this manner, 1 part of trypsin should digest at least 75 parts of casein.

As originally suggested, this Fuld-Gross test employed a much weaker casein solution; but there is a distinct advantage in using as much casein as here recommended, and any ferment of reasonable strength should react with this weight of casein. The weak casein solutions are useful in testing very weak tryptic solutions, in scientific investigations mainly.

*Amylopsin*, the starch-digesting ferment of the pancreas, converts starch into maltose and forms a small amount of dextrose. It acts best at a temperature of about 40 C. and in a slightly alkaline medium. It is very sensitive to free acids. Even slight degrees of acidity check the action and destroy the ferment.

Amylopsin is rarely used for the digestion of starch in the preparation of food, because malt diastase is preferable. It is not likely to be of service to secure the digestion of starch in the intestine because it is destroyed in the stomach. It has been proposed by Beard to be injected along with trypsin in the hope of exerting a destructive action on the cells of malignant tumors. No sufficient evidence has been advanced to warrant a belief in its efficacy.

*Determination of Amylolytic Value.*—(For diastases, malt and pancreas preparations.) The Council does not endorse the methods which are based on the time of change from blue to red given by iodine, or the time of disappearance of all color, but instead it has adopted as the standard the amount of starch that can be converted to colorless end-point in ten minutes, by a given weight of the product, working according to the details described. (J. A. M. A., July 11, 1908, p. 140, and *Jour. Chem. Soc.* 30:798, 1908.)

### Proteolytic Ferments

#### PEPSIN GROUP, INCLUDING RENNIN

**ELIXIR OF ENZYMES.**—A solution containing pepsin and rennet in a menstruum containing 20 per cent. of alcohol.

*Actions and Uses.*—This elixir is claimed to be useful as an aid to digestion and as a vehicle for various drugs.

*Dosage.*—From 4 to 8 Cc. (1 to 2 fluidrachms) with meals; for children in proportion.

Manufactured by Armour & Co., Chicago.

Elixir of enzymes is a light yellow, palatable, liquid preparation. One part digests about 20 parts of coagulated egg albumin in two and one-half hours. Eight Cc. (2 fluidrachms) coagulate 500 Cc. (1 pint) of milk in a few minutes.

**ENZYMOL.**—An extract prepared from the fresh animal stomach, stated to contain the activated gastric enzyme in association with the soluble constituents with which the pro-enzyme is naturally associated. It is free from alcohol, contains a trace of thymol, and has an acidity due to combined hydrochloric acid equivalent to 0.26 to 0.3 per cent. of actual hydrochloric acid. It is adjusted to a definite proteolytic power by the U. S. P. assay method for pepsin, and contains 25 per cent. of glycerin by weight.

*Actions and Uses.*—Enzymol is stated to be useful as an application to old sores, ulcers and slow-healing wounds. It is said to correct offensive odors, to exert a solvent action

on pus and sloughing and necrotic tissue, and to impart a healing stimulus. It is stated to have been effective in cases which have long remained unhealed and have resisted treatment.

*Dosage.*—It is made ready for use by the addition of one-half to one or two volumes of water; for the solution of necrotic and carious bone, and in some large abscess cavities, it is advised that the preparation be diluted with two volumes of 0.2 per cent. solution of hydrochloric acid. A small vial, containing diluted hydrochloric acid and a pipette for measuring, accompanies the package of enzymol.

Manufactured by Fairchild Bros. & Foster, New York. No U. S. patent. U. S. trademark No. 44,769.

Enzymol is a light straw-colored fluid.

The presence of the various groups of proteins is shown by the following reactions: Upon heating to boiling the fluid gives a copious coagulation; the filtrate from this gives a marked precipitate with phosphotungstic acid; the protein derivatives remaining in solution may be determined by silver nitrate and barium oxide according to Hall. Alcohol in excess likewise gives a copious precipitate. The proteolytic power for pepsin when acidified and tested by the method of the U. S. P. should be such that 4 Cc. will dissolve 800 Gm. of coagulated egg-albumin in two and one-half hours.

**ESSENCE OF PEPSIN-FAIRCHILD.**—An aromatized faintly acid liquid obtained by direct extractions from the pig stomach glands, and from the lining membrane of the calf stomach, and containing the entire soluble constituents of the fresh stomach glands—the proteolytic and milk-curdling enzymes, coagulable nucleoproteids, organic and inorganic extractives—and 18.5 per cent. alcohol.

*Actions and Uses.*—Essence of pepsin-Fairchild is claimed by the manufacturers to be of value in disorders of stomach digestion, as a vehicle for the administration of drugs, and in the preparation of whey and other milk food for the infant and invalid.

*Dosage.*—4 Cc. (1 fluidrachm) or more.

Manufactured by Fairchild Bros. & Foster, New York.

Essence of pepsin-Fairchild is prepared by direct extraction from the entire mucous membrane of the fresh stomach.

One Cc. will curdle 250 Cc. of milk at 38 C. in a few minutes, and dissolve 50 Gm. of coagulated egg albumin when tested according to the directions of the U. S. P.

**GASTRON.**—A solution of the gastric tissue juice obtained by direct extraction from the mucosa of the fresh stomach of the pig and containing the activated principles of the gastric cells, the enzymes and the associated organic and inorganic constituents in an acid, aromatized menstruum containing 25 per cent. glycerin by weight. It has an acidity corresponding

approximately to 0.25 per cent. absolute hydrochloric acid, and 1 Cc. dissolves 200 Gm. coagulated egg albumin under standard conditions.

*Actions and Uses.*—Gastron is claimed to exhibit the characteristic enzymic properties of gastric secretion. It is designed to present in a stable form a complete gastric gland extract for use in disorders of gastric functions.

*Dosage.*—From 4 to 8 Cc. (1 to 2 fluidrachms) diluted with a little cold water or with acidulated water. It may be administered before, in divided doses during, or after meals.

Manufactured by Fairchild Bros. & Foster, New York. No U. S. patent. U. S. trademark No. 65,397.

Gastron is a viscid, slightly opaque, straw-colored fluid. Heat and strong alcohol cause coagulation of gastron.

One Cc. of gastron in water acidulated to 0.3 per cent. hydrochloric acid is capable of dissolving 200 Gm. coagulated fresh egg-albumin when treated according to the method for the valuation of pepsin of the U. S. P.

#### TRYPSIN GROUP

**TRYPSIN.**—The proteolytic enzyme of the pancreas, separated to a considerable extent from the other enzymes and constituents of the gland.

*Actions and Uses.*—See discussion of typtic ferments in preceding general article, Ferments, Digestive.

**Trypsin-Armour.**—It is stated that trypsin-Armour is standardized so that one part digests at least one hundred parts of casein according to the Fuld-Gross method.

*Dosage.*—Trypsin-Armour is applied locally by means of a brush or as a spray. About 0.4 Gm. (6 grains) are mixed with 0.125 Gm. (2 grains) sodium bicarbonate and triturated in a mortar while adding 1 or 2 drachms of distilled water, then warmed to from 38 to 40.6 C. and applied immediately. The application may be repeated several times an hour if necessary, a fresh solution being made before each application. The internal dose is 0.125 Gm. (2 grains) or more three times daily. It should not be used for hypodermic injection.

Manufactured by Armour & Co., Chicago. No U. S. patent or trademark.

Trypsin-Armour is prepared from the fresh pancreas of hogs with the view of retaining the proteolytic ferment in an especially active condition. It has been activated by enterokinase.

It is a light yellow powder, possessing a faint odor and a meat-like taste. It is not completely soluble in water at once, but dissolves almost entirely in time.

**Trypsin-Fairchild.**—When tested by the Fuld-Gross method it is stated that trypsin-Fairchild converts 200 times its weight of casein to the standard end point.



*Dosage.*—Trypsin-Fairchild may be given in doses of 1 grain (equal to from 4 to 5 grains Pancreatin, U. S. P.) and upward, best in a capsule with some diluent, as milk-sugar, and if indicated, with sodium bicarbonate. It is locally applied in solution or after trituration of the trypsin with some appropriate diffusible powder.

Manufactured by Fairchild Brothers & Foster, New York. No U. S. patent or trademark.

Trypsin-Fairchild, is a fine dry powder, in which form the enzyme is permanent when protected from moisture. It is slowly but not completely soluble in water.

Trypsin-Fairchild, has from four to five times the strength of Pancreatin, U. S. P. The tryptic power of Fairchild's trypsin by the method proposed by Sir William Roberts is 10,000 units.

**HOLADIN.**—See under Mixtures.

**PANASE.**—See under Mixtures.

#### Amylolytic Ferments

**DIAZYME ESSENCE.**—A liquid stated to contain the amylolytic enzyme of the pancreas, devoid of trypsin and lipase, in a menstruum containing 18.5 per cent. of alcohol by volume.

*Actions and Uses.*—Diazyme is capable of digesting starch and is claimed to be useful to compensate for deficient salivary and pancreatic action in the digestion of starch.

*Dosage.*—From 4 to 8 Cc. (1 to 2 fluidrachms).

Manufactured by Fairchild Bros. & Foster, New York. U. S. trademark No. 44,878.

Diazyme essence is an amber fluid of aromatic taste and odor and slightly acid reaction.

One Cc. will convert 200 Gm. of pure starch mucilage, containing 8 Gm. of dry starch, the mixture being kept at 40 C., so that the solution will cease to give a color reaction with iodine at the end of ten minutes.

**DIAZYME GLYCEROLE.**—A liquid stated to contain the amylolytic enzyme of the pancreas, devoid of trypsin and lipase, in a menstruum containing about 60 per cent. of glycerin by volume.

*Actions, Uses and Dosage.*—See Diazyme Essence.

Manufactured by Fairchild Bros. & Foster, New York. U. S. trademark No. 44,878.

Diazyme glycerole is a dense amber fluid, of agreeable taste and odor, and of slightly acid reaction.

One Cc. will convert at 40 C. 200 Gm. of pure starch mucilage, containing 8 Gm. dry starch, so that the solution will cease to give a color reaction with iodine in ten minutes.

**HOLADIN.**—See under Mixtures.

**PANASE.**—See under Mixtures.

## Mixtures

**HOLADIN.**—*Extractum Pancreaticum .Integrum.*—An extract of the entire pancreas containing all the constituents of the gland and exhibiting great potency in respect to the several known enzymes, trypsin, amyllopsin, lipase and the milk-curdling ferment.

*Actions and Uses.*—Holadin has power to digest starch and proteids and to split fats. It is claimed to be useful in various diseases in which digestion of food is imperfect.

*Dosage.*—Holadin is furnished only in capsules, each capsule containing approximately 3 grains. One capsule should be given about three hours after meals and 1 capsule at bedtime. The dose can be gradually increased to 2 or 3 capsules at a time.

Manufactured by Fairchild Bros. & Foster, New York. U. S. trademark No. 60,625.

Holadin is a grayish-white powder, slightly aromatized, somewhat hygroscopic, freely but not wholly soluble in water.

*Tests.*—The tryptic power is tested as follows: 0.1 Gm. is placed in a flask, mixed by agitation with 25 Cc. of tepid water containing 0.2 Gm. sodium bicarbonate; at once 100 Cc. of milk at 40 C. is added, and then the flask kept in a water-bath at 40 C. From time to time small portions are withdrawn in a beaker glass, when the addition of a few drops of dilute acetic acid will show a constant diminution in the volume and character of the curd until finally only minute, flocculent coagula are observed. Holadin should not remain in contact with sodium bicarbonate for more than a brief interval before adding the milk, as its enzymic power is rapidly decreased thereby. To test for the fat-splitting action, 0.1 Gm. of holadin is mixed with 25 Cc. of water and 100 Cc. of milk and maintained at 40 C. In about fifteen minutes the presence of fatty acids can be detected by odor and taste and confirmed by chemical tests.

The action of the milk-curdling ferment is shown in the following way: 0.02 Gm. holadin is mixed with 10 Cc. water in a beaker and then 100 Cc. fresh milk, previously warmed to 40 C., poured on, with sufficient stirring to mix thoroughly, and the mixture digested, without agitation, in a water-bath at 40 C. In a few minutes the milk will begin to show the characteristic evidences of curdling similar to that produced by the milk-curdling ferment of the gastric juice. When the milk, however, has acquired a semisolid jelly-like consistency, if it then be stirred constantly with a glass rod, the curd will break down, become diffusible and in time disappear, a behavior which is in marked contrast to the action of the milk-curdling ferment of the gastric juice which causes the formation of a firm curd, easily separable from the whey. The starch-converting power is determined as follows: Triturate 15 Gm. of arrowroot or potato starch with 500 Cc. of distilled water, boil for ten minutes, allow to cool, and make up to 500 Cc. with distilled water. Prepare an iodine test solution by diluting 0.5 Cc. of liquor iodi compositus, U. S. P., with water to make 500 Cc. and have ready sufficient number of tubes containing an equal quantity of this solution. If holadin be treated as given below the results should indicate that it converts 135 times its own weight of starch in ten minutes and 600 times its weight in sixty minutes. Triturate 0.13 Gm. holadin in a perfectly dry mortar with 1.170 Gm. of lactose. Place 100 Gm. of the starch mucilage in a Florence flask in a water-bath at 40 C. and mark "A"; place in

the water-bath also another flask of the same content and mark "B." Add to flask A 0.2 Gm. of the holadin triturate; to flask B add 0.05 Gm. of the holadin triturate; maintain both flasks in the water-bath at 40 C. At the expiration of ten minutes withdraw from flask A 1 drop of the solution and add to one of the tubes of the iodine solution, when no coloration will occur. At the end of fifty minutes take 1 drop from flask B and add to one of the tubes of iodine solution, and at intervals of a few minutes repeat this; in about sixty minutes, no coloration, or at the most a very faint coloration, will appear. Under these circumstances 1 grain of holadin will convert 135 grains of starch completely in ten minutes, and 600 grains in about sixty minutes.

**PANASE.** A combination of the digestive enzymes of the pancreas derived from the pancreatic gland of the pig.

*Actions and Uses.*—Panase is intended to be used in cases in which it is believed that the enzymes of the pancreas are deficient or in which it is desired to hasten the digestion of starch.

*Dosage.*—0.13 Gm. (2 grains) or more.

Manufactured by Frederick Stearns & Co., Detroit.

*Panase Essence.*—*Essentia Panasi.*—A mixture containing in each 100 Cc., 4 Gm. of panase in a menstruum containing 14 per cent. alcohol and 12.5 per cent. of glycerin with small amount of flavoring matter and sugar. Dose 4 Cc. (1 fluidrachm) containing 0.16 Gm. (2¼ grains) of panase.

*Panase Tablets.*—Each tablet contains panase, 0.13 Gm. (2 grains).

Panase is prepared by macerating the gland and extracting the enzymes together with a small amount of the proteid matter of the gland.

Panase is a light, yellowish-white powder having a slight odor and somewhat mucilaginous taste. It is not entirely soluble in water or glycerin, owing to the small amount of protein present. Filtration of its solution, however, does not impair its digestive activity.

Panase should possess the diastasic, proteolytic, milk-curdling and fat-splitting properties of the pancreatic juice. It converts 200 times its weight of hydrous starch to loss of blue iodine reaction in ten minutes when tested according to the method of Blome (*Pharm. Rev.*, 1906, xxiv, 260). According to the method adopted by the Council it converts 113 parts of anhydrous starch to the colorless end point in ten minutes (*J. A. M. A.*, July 11, 1908, p. 140; *Jour. Am. Chem. Soc.*, May, 1908, p. 798).

It is incompatible with strong alcohol, acids, alkalies and other substances which destroy the activity of ferments.

## FIBRIN FERMENT AND THROMBOPLASTIC SUBSTANCES (KEPHALIN)

The clotting of blood (that is, the transformation of the fibrinogen of circulating blood into the insoluble fibrin of blood-clot) has been shown to be due to the action of the fibrin ferment (thrombin) on the fibrinogen of the blood.

The fibrin ferment of thrombin exists in the blood in the form of its forerunner (prothrombin) which is acted on by the calcium salts and converted into thrombin. Besides calcium salts, however, another factor is necessary. In spite of a sufficient supply of calcium salts, blood does not clot spontaneously within the vessels. This other factor may be furnished from the breaking down of blood cells or blood platelets or from the pieces of tissues that are cut or badly injured. It has been designated as "zymoplastic" substance by Schmidt, as "thrombokinase" by Morowitz, and as "thromboplastic substance" or "thromboplastin" by Howell (*Am. J. Physiol.*, 31: 1, 1912). Howell believes that the reason that blood does not coagulate within the vessels is that the prothrombin exists here in combination with an antithrombin, which prevents it from acting. He believes that when blood is shed or flows over injured tissue the thromboplastin derived from blood cells, blood platelets or tissue cells combines with this antithrombin, liberating the prothrombin from combination with the latter. The prothrombin thus liberated now combines with the calcium salts, is converted into thrombin and converts the fibrinogen of the plasma into fibrin, causing coagulation to set in. Howell has shown that thromboplastin or "thromboplastic substance" from every source in which he has investigated it gives the reactions of the lipoid kephalin—the main lipoid of the brain. It is soluble in ether, but insoluble in water, alcohol and acetone, and kephalin prepared from the brain possesses the same action.

*Actions and Uses.*—Preparations containing thromboplastin are said to be useful when applied locally in the treatment of hemorrhages, especially hemorrhages from oozing surfaces, scar tissues and nosebleeds, and in surgery of the bones, glands, nose and throat. When injected subcutaneously or intravenously such preparations are said to shorten the coagulation time of the blood for a period of about twenty-four hours, but there may be a certain danger of a negative phase setting in. Such injections are contraindicated in cases in which there is a tendency to thrombosis or embolism; for example, in arteriosclerosis, aneurysm, heart weakness, phlebitis, certain stages of syphilis, and in varicose veins. Injections of kephalin seem to have little effect in hemophilia (Hurwitz and Lucas: *Arch. Int. Med.*, 17: 543, 1916). Preparations should be standardized by testing on specimens of blood in vitro, which should be able to bring the coagulation time to about one third of its original length; they should be proven sterile, particularly if intended for intravenous use.

**BRAIN LIPOID.**—Impure Kephalin.—An ether extract of the brain of the ox, or other mammal, prepared according to the method of Howell as applied in practice by Hirschfelde (*Lancet*, 2: 542, 1915) (see below).



*Actions and Uses.*—See preceding general article, Fibrin Ferment and Thromboplastic Substances (Kephalin).

*Dosage.*—Brain lipid may be smeared on gauze sponges, pledgets, or on the tissues themselves; or an emulsion may be prepared by shaking up with physiologic sodium chloride solution and used in the same way or sponged over the tissues.

For use in an office or dispensary, the ether extract suffices and can be kept ready for use for some time (several months) in a sterile dropper bottle from which an opalescent emulsion can be prepared at a moment's notice by dropping 10 to 30 drops into an ounce of physiological sodium chloride solution and then shaking up. This solution can also be dispensed from drug stores, provided the opening in the stopper of the dropper bottle is kept slightly open to prevent blowing off of the ether on shaking or heating.

Brain lipid (impure kephalin) is prepared from ox brain which is run through a hashing machine, then covered with 3 volumes of alcohol, shaken up two or three times, and the excess of alcohol then poured off and squeezed out gently through linen, care being taken to avoid great force in wringing out the alcohol, as this tends to break up the brain tissue into very finely divided particles which pass through the filter. The residue is then covered with 3 volumes of ether, shaken vigorously and filtered first through cotton and then through filter paper. The clear filtrate thus obtained is evaporated to dryness over a water bath and a yellow residue of fatty appearance and consistency remains. (This residue consists largely of kephalin, but though the latter is not in the pure state, it is extremely active in accelerating the clotting of blood *in vitro*).

The method of preparation renders it sterile. It can be transferred on a sterile spatula or knife blade to sterile vessels. It retains its activity for several weeks.

(The impurities present, largely the lecithins and myelins, do not materially detract from the activity of the kephalin, but, on the contrary, facilitate its emulsification in sodium chloride solution and thus facilitate its intimate miscibility with blood.)

**Kephalin-Armour.**—The hemostatic phosphatid obtained from spinal cord and brain tissue. It is essentially the same as Brain Lipid.

*Action and Uses.*—See general article, Fibrin Ferments and Thromboplastic Substances (Kephalin).

*Dosage.*—0.1 to 0.2 per cent. suspensions of kephalin-Armour in sterile physiologic sodium chloride solution is applied freely to bleeding or oozing surfaces.

Manufactured by Armour and Company, Chicago. No U. S. patent or trademark.

The brain and spinal cord of mammals is desiccated *in vacuo* and the crude phosphatids extracted by means of petroleum ether. This liquid is concentrated and then precipitated with an excess of acetone. The precipitate is extracted with acetone and then with alcohol. The residue is dried and dissolved in ether and the ether solution evaporated to dryness at a low temperature.

Kephalin-Armour is an amorphous, yellowish substance of characteristic odor and taste. It is readily soluble in ether and chloroform, slightly soluble in alcohol and insoluble in acetone. In neutral aqueous solution it forms an opalescent emulsion. The blood clotting properties of kephalin-Armour are not destroyed by boiling aqueous suspensions of it.

One part kephalin-Armour will coagulate 1000 parts oxalated blood plasma in from one to two minutes when tested as follows: 1 Cc. of a 5 per cent. solution of kephalin-Armour in ether is added to 25 Cc. of physiological sodium chloride solution and the mixture shaken until a uniform suspension results. 5 Cc. of this suspension is mixed in a large test tube with an equal volume of blood serum. Ten Cc. of oxalated blood plasma (1 Gm. sodium oxalate in 100 Cc. water added to 900 Cc. fresh blood) are then added and mixed by inverting the test tube twice. The mixture is rapidly transferred to a shallow porcelain dish: it should curdle in from one to two minutes. All solutions used in the preceding test should be made freshly and the temperature of the liquids and the porcelain dish should be maintained at 38 C.

**SOLUTION BRAIN EXTRACT.**—Solution Thromboplastin-Hess.—An extract of cattle brain in physiologic sodium chloride solution prepared by the method of Hess (J. A. M. A., 66: 558, 1914, Note 2).

*Actions and Uses.*—See preceding general article, Fibrin Ferment and Thromboplastic Substances (Kephalin).

*Dosage.*—The solution may be applied directly to the bleeding tissues or sprayed on them, or a sponge or tampon may be immersed in it and then pressed on the bleeding surface.

Cattle brains are obtained fresh from the slaughtering-house, stripped of their membranes, washed in running water and weighed. They are then passed through a meat chopping machine three times, and an equal amount of physiologic sodium chloride solution is added. This suspension is allowed to remain in the refrigerator for forty-eight hours, and it is then twice pressed through cheese-cloth. This extract, which contains fine suspension of tissue in addition to tissue juice, is diluted with one half its volume of physiologic sodium chloride solution. Cresol is then added in proper proportion so that the finished preparation contains 0.3 per cent. It maintains its hemostatic potency for some time (several months). (Since cresol is not a perfect antiseptic, the sterility of this preparation cannot be guaranteed.)

**Thromboplastin Solution-Armour.**—An extract of cattle brain in physiologic sodium chloride solution prepared according to the method of Hess. It complies with the description of Solution Brain Extract.

*Action and Uses.*—See general article, Fibrin Ferments and Thromboplastic Substances (Kephalin).

*Dosage.*—See Solution Brain Extract. Thromboplastin solution-Armour is marketed in 25 Cc. vials which bear an expiration date, after which time the contents should not be used.

Manufactured by Armour & Co., Chicago. No U. S. patent or trademark.

One part thromboplastin solution-Armour will coagulate 100 parts of oxalated blood plasma in less than one minute when tested as follows:

To 0.5 Cc. thromboplastin solution-Armour is added 24.5 Cc. physiological sodium chloric solution and the mixture shaken until a uniform emulsion results. Of this suspension 5 Cc. is mixed in a graduated cylinder with an equal volume of blood serum. To this is added 10 Cc. of oxalated blood plasma (1 Gm. sodium oxalate in 100 Cc. of water, added to 900 Cc. of fresh blood) and mixed by inverting the cylinder twice. The mixture is rapidly transferred to a shallow dish; it should coagulate in less than one minute. For this test, all solutions must be made freshly and the temperature of the liquids maintained at 38 C.

**Thromboplastin-Squibb.**—An extract of cattle brain in physiologic sodium chloride solution prepared according to the method of Hess. It complies with the description of Solution Brain Extract.

*Actions and Uses.*—See general article, Fibrin Ferments and Thromboplastic Substances (Kephalin).

*Dosage.*—See Solution Brain Extract. Thromboplastin-Squibb is marketed in 20 Cc. vials. It is claimed that no loss of potency could be detected in a specimen of thromboplastin-Squibb over eighteen months old.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

**COAGULEN-CIBA.**—Coagulen, Kocher-Fonio.—Coagulin, Kocher-Fonio.—An extract said to be prepared from blood-platelets and to contain thromboplastic substance (cytozym, thrombokinas, thrombozym), mixed with lactose, 1 Gm. representing 20 Gm. dried blood.

*Actions and Uses.*—See general article, Fibrin Ferment and Thromboplastic Substances (Kephalin).

*Dosage.*—Solutions of coagulen-Ciba, generally 5 per cent., are used locally, intramuscularly and intravenously. The subcutaneous or intravenous injection is contraindicated in cases in which there is a tendency to thrombosis or embolism, for example, in arteriosclerosis, aneurysm, heart weakness, phlebitis, certain stages of lues and in varicose veins. Solutions should be freshly made by dissolving in physiologic salt solution and sterilizing this by boiling for three minutes. In urgent cases ordinary water may be used as a solvent.

Manufactured by the Society of Chemical Industry, Basle, Switzerland (A. Klipstein and Co., New York). U. S. patent No. 1,240,694 (Sept. 18, 1917; expires 1934). U. S. trademark No. 99,809.

*Sterile Solution Coagulen-Ciba (3 per cent.), 1.5 Cc. Ampoules.*—Each ampule contains 1.5 Cc. of a 3 per cent. sterile solution of coagulen-Ciba.

*Sterile Solution Coagulen-Ciba (3 per cent.), 20 Cc. Ampoules.*—Each ampule contains 20 Cc. of a 3 per cent. sterile solution of coagulen-Ciba.

*Tablets Coagulen-Ciba, 0.5 Gm.*—Each compressed tablet contains coagulen-Ciba 0.5 Gm. and sodium chloride 0.46 Gm.

Coagulen-Ciba is a yellowish, granular powder, having a slight odor and a sweet taste. It is very soluble in water and such solution may be boiled for two or three minutes without decomposition. The active principle of coagulen-Ciba is also soluble in alcohol and chloroform.

## FILICIC ACID AND RELATED SUBSTANCES

Aspidium and pharmaceutical preparations thereof have long been used as teniafuges. The most recent work indicates that aspidium probably contains the following constituents, in approximately the amount indicated: filicic acid, 3.5 per cent.; flavaspidic acid, 2.5 per cent.; albaspidin, 0.05 per cent.; aspidinol, 0.10 per cent.; flavaspidin, 0.10 per cent.; amorphous acid, 5.0 per cent. and filicic nigrine, 60 per cent. These substances are, for the greater part, derivatives of phloroglucinol, and some of them are ketones possessing acid characters.

The various formulas assigned to the filicic acids and the different results reported regarding their physiologic activity have given rise to much confusion, leaving the chemistry in an unsettled condition. One of the first formulas assigned to filicic acid is that of Luck ( $C_{28}H_{30}O_9$ ), which differs considerably from the formula  $C_{14}H_{18}O_5$ , given this substance by Grabowski, and  $C_{14}H_{16}O_5$ , as suggested by Dacoma. Later two forms, a crystalline and an amorphous filicic acid, were recognized by Poulson, who suggested the formula  $C_{28}H_{40}O_{12}$  for the crystalline filicic acid and  $C_{36}H_{42}O_{13}$  for the amorphous acid, which latter he considered as the active therapeutic principle of aspidium. Poulson believed the crystalline acid to be the anhydride of the amorphous acid. More recently, Gallas has stated the formula for both the crystalline and the amorphous filicic acid to be  $C_{18}H_{22}O_6$ . Gallas and later Kraft concluded that one form of the acid was the lactone of the other form. Filicinic acid, which has the formula  $C_8H_{10}O_3$ , is sometimes confused with filicic acid. Besides a difference in the theories regarding the constitution of the various filicic acids, there has been considerable controversy over the anthelmintic properties of these substances.

Our knowledge of the subject is very imperfect, but the majority of authors still accept filicic acid as one of the active constituents of aspidium.



**FLUORESCEIN.**—**Fluoresceinum.** — Resorcinolphthalein (a term not strictly correct but commonly used).—Dioxy-fluoran. —  $O:(C_6H_5OH)_2:C_6H_4.COO.$ —The anhydride of fluoresceinic acid,  $O:(C_6H_5OH)_2:C(OH).C_6H_4(COOH).$

*Actions and Uses*—The soluble sodium salt of fluorescein (fluorescein 2 Gm., sodium bicarbonate 3 Gm., water to make 100 Cc.) has been used for the diagnosis of corneal lesions and detection of minute foreign bodies imbedded in the cornea. While a weak solution of fluorescein will not stain the normal cornea, ulcers or parts deprived of epithelium will become green and remain so for a time; foreign bodies will appear surrounded by a green ring; loss of substance in the conjunctiva is indicated by a yellow hue. Fluorescein also reveals defects or disease of the endothelium of the cornea, producing a deep coloration of the diseased area.

*Tabloid (Ophthalmic) Fluorescein, B.-W. & Co.*—Each tablet contains fluorescein 0.00026 Gm. (1/250 grain) in combination with sodium and weighs 0.0032 Gm. (1/20 grain). Prepared by Burroughs Wellcome & Co., London, England, and New York.

Fluorescein is prepared by the fusion of phthalic anhydride and resorcinol at from 195 to 200 C. till the mass becomes solid. This is extracted with water and the residue dissolved in potassium hydroxide solution, which is then filtered and the fluorescein precipitated with acid.

Fluorescein is an orange red powder, insoluble in water, ether, chloroform and benzol; soluble in hot glacial acetic acid and boiling alcohol. It dissolves in alkaline solution with formation of a salt. The alkaline solution by transmitted light is red; by reflected light it has a green fluorescence even in very dilute solutions. When fluorescein is boiled with chalk and water the calcium salt of fluorescein is formed, which is recognized by its red-brown color and green sheen.

**Fluorescein-Merck.**—A nonproprietary brand complying with the standards for fluorescein.

Merck & Co., New York, distributors.

## FORMALDEHYDE PREPARATIONS AND COMPOUNDS WHICH LIBERATE FORMALDEHYDE

The antiseptic actions of formaldehyde cannot be utilized directly on the body, because of the irritant and coagulant effects. Attempts have been made to avoid these effects by combining the formaldehyde in such a way as to cause it to be liberated very gradually. The results have been rather disappointing, because it is difficult, if not impossible, to secure just that degree of stability in which the formaldehyde will be liberated in concentrations sufficient to maintain the antiseptic action, but not sufficient to become irritant. Hexa-

methylenamin is a notable exception; but its effects are confined to acid fluids, and therefore essentially to the urine. Other compounds are effective mainly through the other constituents with which the formaldehyde is combined, rather than through the formaldehyde itself.

The wide reactivity of formaldehyde gives the possibility of a great variety of compounds: with proteins (glutol); carbohydrates; acetamide (formicin); phenols and aromatic derivatives (empyroform; tannoform), etc. Hexamethylenamin does not contain formaldehyde as such, but generates it under certain conditions.

The following preparations and compounds are included in N. N. R.:

**Formaldehyde Preparations:** solution of formaldehyde, formalin, paraformaldehyde and trioxymethylene.

**The Simpler Formaldehyde Compound:** formicin.

Hexamethylenamine (aminoform, formin and urotropine), and Hexamethylenamine Compounds: amphotropin, hexamethylenamine methylene citrate, helmitol and hexalet.

### Formaldehyde Preparations

**PARAFORMALDEHYDE.**—For description see U. S. Pharmacopeia under Paraformaldehydum.

*Actions and Uses.*—Antiseptic and escharotic. Its internal administration is inadvisable, since it has produced serious effects (Fraenkel, *Arzneimittelsynthese*, Ed. 3, p. 622). It is used chiefly to generate formaldehyde by heating, for disinfection.

*Dosage.*—Internally, from 0.3 to 1 Gm. (5 to 15 grains); externally (for warts), in 10 per cent. suspension in collodion.

**Trioxymethylene.**—A proprietary name applied to paraformaldehyde.

Merck & Co., New York, distributors. No U. S. patent or trademark.

**SOLUTION OF FORMALDEHYDE.**—For description see U. S. Pharmacopeia under Liquor Formaldehydi.

*Actions, Uses and Dosage.*—See "Useful Drugs."

**Formalin.**—A name applied to solution of formaldehyde, U. S. P.

Schering & Glatz, Inc., New York, distributors. U. S. trademark No. 65,625.

### The Simpler Formaldehyde Compounds

**FORMICIN.** — Formaldehyde-Acetamide. —  $\text{CH}_3\text{C.O.NH.CH}_2\text{OH}$ .—A molecular compound of formaldehyde and acetamide.

*Actions and Uses.*—Solutions of formicin liberate formaldehyde gradually at body temperature, and thus exert a local antiseptic action. Formicin is practically nontoxic and 5 per cent. solutions produce but little irritation.

*Dosage.*—Solutions of from 1 to 5 per cent. are employed as injections into tuberculous and non-tuberculous joints, tissues and abscesses; for bladder irrigation in chronic cystitis 2 per cent. solutions are used; 5 per cent. alcoholic solutions have also been suggested for the disinfection of the skin and hands.

Manufactured by Kalle & Co., A. G., Biebrich a/Rh., Germany (Kalle Color & Chemical Co., New York). German patent No. 164,610. No U. S. patent or trademark.

Formicin is a slightly yellowish, thick, syrupy liquid, having a faint, formaldehyde-like odor and a slightly acid, bitter taste. The specific gravity of formicin should be between 1.14 and 1.18 at 20 C. Formicin is soluble in water, alcohol, chloroform and glycerin; it is nearly insoluble in ether. An aqueous solution of formicin (1:10) has an acid reaction on litmus. At 115 to 120 C. formicin dissociates.

If 1 Cc. of an aqueous solution of formicin (1:10) be mixed with 1 Cc. of a mixture composed of equal volumes of stronger ammonia water, potassium hydroxide test solution and silver nitrate test solution, no immediate darkening should take place; but if the mixture be allowed to stand for some time, or be warmed, darkening occurs, due to the separation of metallic silver. If an aqueous solution of formicin (1:10) be mixed with a 2 per cent. aqueous solution of aniline no immediate turbidity should appear.

## Hexamethylenamine and Hexamethylenamine Compounds

Hexamethylene-tetramine, official as hexamethylenamine, owes its action entirely to the liberation of formaldehyde, which occurs only in acid fluids. It is an active urinary antiseptic, provided that the urine is not secreted in an alkaline state. Recent work (Hanzlik and Collins, *Arch. Int. Med.*, November, 1913; Hanzlik; J. A. M. A., Jan. 24, 1914, p. 295) has shown that no antiseptic effects can occur in the body tissues and fluids which have a neutral or slightly alkaline reaction. Hexamethylenamine apparently is not a uric acid solvent, and in gout it has not given satisfactory results.

Its use as a prophylactic against nephritis, especially in scarlatina, has been recommended by several authors. Yet hexamethylenamine itself may, at least sometimes, act as a renal irritant. The Council deems it a duty to call attention to this fact, and also to the statement of Jochmann that "A prophylactic drug treatment, as with Urotropin, etc., cannot prevent the nephritis" [of scarlatina].

Hexamethylenamine compounds simply possess the actions of hexamethylenamine and of the salts of the acid with which it may be combined.

**HEXAMETHYLENAMINE.**—For description see the U. S. Pharmacopeia under Hexamethylenamina.

*Actions and Uses.*—See general article, Hexamethylenamine and Hexamethylenamine Compounds, above.

**Aminoform.**—A proprietary name applied to Hexamethylenamine, U. S. P.

Sold by C. Bischoff & Co., Inc., New York.

**Formin.**—A proprietary name applied to Hexamethylenamine, U. S. P.

Merck & Co., New York, distributors.

*Formin Tablets*, 5 grains.—Each tablet contains formin 5 grains.

*Formin Tablets*,  $7\frac{1}{2}$  grains.—Each tablet contains formin  $7\frac{1}{2}$  grains.

**Urotropine.**—A proprietary name applied to Hexamethylenamine, U. S. P.

Schering & Glatz, Inc., New York, distributors. U. S. trademark No. 58,394.

*Urotropine Tablets*, 5 grains.—Each tablet contains urotropine, 5 grains.

*Urotropine Tablets*,  $7\frac{1}{2}$  grains.—Each tablet contains urotropine,  $7\frac{1}{2}$  grains.

**AMPHOTROPIN.**—Hexamethylene-Tetramine Camphorate.— $[(CH_2)_6N_4]_2.C_8H_{14}(COOH)_2$ .—A molecular combination of camphoric acid and hexamethylene-tetramine.

*Actions and Uses.*—Amphotropin combines the actions of camphoric acid and hexamethylenamine, but it is claimed that it is free from the subjective gastric disturbances produced by full doses of camphoric acid, and that it is effective in smaller doses (presumably by neutralization and increased solubility of the acid). It acts as a urinary antiseptic, and is said to promote the regeneration of sloughing epithelium. It increases diuresis and the elimination of uric acid in pathologic conditions.

Amphotropin is used similarly to hexamethylenamine against infections of the urinary tract. It is said to be contraindicated in acute cystitis, and in the initial stages of tuberculosis of the urinary organs.

*Dosage.*—0.5 Gm. (8 grains) three times daily. If necessary the dose may be increased to 1 Gm. (15 grains) three times daily.

Manufactured by Farbwerke, vorm. Meister, Lucius & Bruening, Hoechst a.M., Germany (H. A. Metz Laboratories, Inc., New York). U. S. patent No. 1,064,227 (June 10, 1913; expires 1930). U. S. trademark No. 89,917.

*Amphotropin Tablets.*—Each tablet contains amphotropin 0.5 Gm. ( $7\frac{1}{2}$  grains).

Amphotropin is prepared by interaction of a solution of hexamethylene-tetramine and of camphoric acid in a suitable organic solvent and isolation of the resulting product.



Amphotropin is a light, white crystalline powder, soluble in water, alcohol and chloroform, but almost insoluble in ether and benzene. The aqueous solution possesses an acid reaction.

If 10 Cc. of a saturated aqueous solution of amphotropin be treated with 3 Cc. of dilute sulphuric acid a white precipitate will be formed, which after washing and drying should melt at 186 C. If the filtrate from this precipitate be heated the odor of formaldehyde will be apparent. If the same solution be made alkaline with sodium hydroxide and heated, ammonia will be evolved. An aqueous solution (1:20), which should be clear, should not be changed by saturation with hydrogen sulphide or the addition of barium chloride solution. If an aqueous solution of amphotropin be treated with dilute nitric acid it should become not more than opalescent. If an aqueous solution be mixed with an equal volume of sulphuric acid, and then a solution of ferrous sulphate be superimposed, no coloration should appear at the zone of contact of the two solutions. If amphotropin be ignited, no residue should remain. If from 0.2 to 0.3 Gm. of amphotropin be weighed into a flask, and dissolved in from 30 to 40 Cc. of a mixture of equal parts of water and alcohol, the titration of this solution with normal alkali, using phenolphthalein as indicator, should indicate the presence of an equivalent of from 41.5 to 42 per cent. camphoric acid (1 Cc. normal alkali is equivalent to 0.1000 Gm. camphoric acid).

#### HEXAMETHYLENAMINE METHYLENE CITRATE.

—Hexamethylenaminæ Methylencitras.— $C_6H_{12}O_8(CH_2)_6N_4$ .—A compound of hexamethylenamine with anhydromethylene citric acid.

*Actions and Uses.*—Same as those of hexamethylenamine.

*Dosage.*—From 0.65 to 1 Gm. (10 to 15 grains).

Hexamethylenamine methylene citrate is a white, crystalline powder, melting with decomposition at from 165 to 175 C., having an agreeable, acidulous taste and acid reaction. It is soluble in about 10 parts of water but almost insoluble in alcohol and ether. By dilute acids and more easily by alkalis it is decomposed with the liberation of formaldehyde. On addition of 1 per cent. solution of phloroglucin to a solution of hexamethylenamine methylene citrate, followed by sodium hydroxide, the intense rose-red color characteristic of the liberated formaldehyde is developed.

It is incompatible with acids and alkalis.

*Helmitol.*—A proprietary name applied to hexamethylenamine methylene citrate.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent No. 722,275 (March 10, 1903; expires 1920). U. S. trademark No. 39,580.

*Helmitol Tablets, 5 grains.*—Each tablet contains helmitol 0.3 Gm. (5 grains).

**HEXALET.**— $(CH_2)_6N_4.C_6H_5(OH)(COOH)HSO_3 + H_2O$ .—Hexamethylenamine salicylsulphonic acid.

*Actions and Uses.*—Hexalet is dissociated into its constituents in the body, and therefore acts as a urinary antiseptic, as discussed under hexamethylenamine. But little is known about the effects of sulphosalicylic acid; but as the free acid

precipitates proteins, it is claimed that it produces an astringent action on the urinary passages, and would thus be of value in inflammatory conditions of the bladder and urethra.

*Dosage.*—1 Gm. (15 grains) three to six times daily dissolved in a glass of water.

Manufactured by J. D. Riedel, Aktiengesellschaft, Berlin, Germany (Riedel & Co., New York). No U. S. patent. U. S. trademark No. 96,899.

*Hexalet Tablets, 0.5 Gm.*—Each tablet contains hexalet 0.5 Gm. ( $7\frac{1}{2}$  grains).

Hexalet is prepared by the interaction of an alcoholic solution of salicylsulphonic acid and an aqueous solution of hexamethylenamine.

Hexalet is a white odorless crystalline powder, readily soluble in water, slightly soluble in alcohol and with difficulty soluble in ether, having an acid taste.

If an aqueous solution of hexalet be heated to 45 or 50 C., formaldehyde will be liberated. If the residue be now made alkaline with sodium hydroxide and again heated, ammonia will be liberated. If to a dilute aqueous solution of hexalet ferric chloride test solution be added, a violet color will be produced. If to an aqueous solution of hexalet an aqueous albumin solution be added, a white precipitate will form. If to an aqueous solution of hexalet bromine water be added, an orange-colored precipitate will be formed. With the exception of the tannic acid test, hexalet responds to the identity tests of the U. S. Pharmacopeia for hexamethylenamine. If 0.2 to 0.3 Gm. hexalet be fused with 2 Gm. fusion mixture (sodium carbonate and potassium nitrate), the resulting mass dissolved in hydrochloric acid, the addition of barium chloride test solution will produce a white precipitate. If 0.1 to 0.2 Gm. hexalet be moderately heated with 5 Cc. concentrated sulphuric acid, a carmine red color will be produced. If calcium hypochlorite solution be added to an aqueous solution of hexalet, a brown color gradually appears. A 5 per cent. aqueous solution of hexalet should not be changed by saturation with hydrogen sulphide or the addition of barium chloride solution. After acidulation with nitric acid, the addition of silver nitrate solution should produce not more than a slight opalescence. If about 0.5 Gm. hexalet be weighed to a flask, dissolved in 50 Cc. of tenth-normal alkali and phenolphthalein test solution added, the titration of this solution with tenth-normal acid should indicate the presence of from 56.7 to 58.0 per cent. sulphosalicylic acid (1 Cc. of tenth-normal alkali is equivalent to 0.0109 Gm. sulphosalicylic acid).

## FORMIC ACID AND COMPOUNDS

The actions of formic acid resemble those of acetic acid, but formic acid is more volatile, more irritant and more antiseptic. Formic acid and the formates are much more resistant to oxidation in the body than acetic acid and the acetates, and the formates are therefore excreted to a large extent as such in the urine. These have an irritant action on the kidneys and urinary tract, and are diuretic. Large doses cause methemoglobinemia, but the toxicity is rather low. Formic acid and the formates have no effect on the general circulation or on the motor system, as has been claimed. They have been lauded in a great variety of disorders, but there is no good evidence that their internal use produces any benefits other than psychic. The external use of formic acid as a counterirritant is rational, but it possesses no special advantage over other volatile acids.

**FORMIC ACID.**—*Acidum Formicum.*—A liquid containing from 24 to 25 per cent. of anhydrous formic acid ( $\text{HCOOH}$ ).

*Actions and Uses.*—See preceding general article, Formic Acid and Compounds.

*Dosage.*—Internally, from 1 to 20 drops of the 25 per cent. acid, largely diluted; or from 0.1 to 0.25 Gm. ( $1\frac{1}{2}$  to 4 grains) of sodium formate. Externally usually in a solution containing 1 per cent. of the absolute acid in alcohol or diluted alcohol.

Formic acid is a clear, colorless liquid possessing a sharp acid odor and taste. It has a specific gravity of from 1.058 to 1.061.

With lead acetate, formic acid produces a white crystalline precipitate. On warming with silver nitrate a gray turbidity and with mercuric chloride a white turbidity is produced. A solution (1:10) after the addition of a few drops of nitric acid should yield no precipitate with silver nitrate or barium chloride; and after neutralizing, with ammonia water, calcium chloride or hydrogen sulphide should produce no precipitate. If 1 Cc. formic acid is mixed with 5 Cc. water and 1.5 Gm. yellow mercuric oxide warmed on the water-bath with agitation until evolution of gas ceases, the mixture, when filtered, will yield a filtrate which should not react acid to litmus (acetic acid). If 5 to 6 Cc. formic acid be titrated with normal alkali, the alkali consumed should indicate the presence of not less than 254 Gm. anhydrous formic acid per liter. Each cubic centimeter of normal alkali is equivalent to 0.046 Gm. anhydrous formic acid ( $\text{HCOOH}$ ). The titrated solution should yield no empyreumatic or sharp odor.

**Formic Acid-Merck.**—A nonproprietary brand complying with the standards for formic acid.

Merck & Co., New York, distributors.

## HYDROCHLORIC ACID AND SUBSTITUTES

Several solid substances have been introduced as medicinal substitutes for hydrochloric acid. It is claimed that these have the action of the free acid in the stomach, but are without the marked acid taste. They also permit the administration of the acid in dry form.

These bodies contain hydrochloric acid in combination with organic substances from which the free acid is readily split off. The physiologic activity of these compounds varies in marked degree with the separability of the hydrochloric acid. The dissociation of the hydrochloric acid, on which the practical value depends, is in some cases nearly complete in aqueous solution, but is much less marked in the case of the large protein-like complexes.

*Actions and Uses.*—It seems to be possible to secure the antiseptic and digestive action of free hydrochloric acid from some of these products, while from others the liberation of the halogen acid is probably insufficient to accomplish these ends in any marked degree.

**BETAINE HYDROCHLORIDE.**—*Betainæ Hydrochloridum.*— $C_5H_{11}NO_2.HCl$ .—The hydrochloride of betaine.

*Actions and Uses.*—In the dry state betaine hydrochloride does not split off hydrochloric acid at ordinary or high temperature, but when dissolved in water there is a gradual liberation of the acid. It, therefore, represents a very convenient method of administering hydrochloric acid.

It is used for the same purpose as hydrochloric acid.

*Dosage.*—0.5 Gm. (8 grains) which corresponds to about 1.1 Cc. (18 minims) of diluted hydrochloric acid U. S. P., to be taken dissolved in water.

Betaine hydrochloride is prepared by the action of hydrochloric acid on betaine.

It consists of colorless crystals, freely soluble in water. It contains 23.8 per cent. absolute hydrochloric acid.

**Acidol.**—A proprietary preparation complying with the standards for betaine hydrochloride.

Manufactured by the Actiengesellschaft für Anilin-Fabrikation, Berlin, Germany (The Bayer Company, Inc., New York). No U. S. patent. U. S. trademark No. 60,783.

*Acidol Tablets, 8 grains.*—Each tablet contains acidol 0.5 Gm. (8 grains).

*Acidol Pepsin Tablets, Mild.*—Each tablet contains pepsin 0.2 Gm. (3 grains) and acidol 0.05 Gm. (1 grain). U. S. patent No. 806,615 (Dec. 5, 1905; expires 1922).

*Acidol Pepsin Tablets, Strong.*—Each tablet contains pepsin 0.1 Gm. ( $1\frac{1}{2}$  grain) and acidol 0.4 Gm. (6 grains). U. S. patent No. 806,615 (Dec. 5, 1905; expires 1922).

**Betaine Hydrochloride-Roche.**—A nonproprietary brand complying with the standards for betaine hydrochloride.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York).

## HYPOCHLORITES AND HYPOCHLORITE SUBSTITUTES

The germicidal action of free chlorine and the hypochlorites is well known. In medicine this action has been utilized by the employment of chlorine water, chlorinated lime, solution of chlorinated soda (Labarraque's solution), and solution of chlorinated potassa (Javelle water).

Hypochlorite preparations are fairly permanent in the presence of alkali, and alkaline hypochlorite preparations have the added advantage that the alkali has a destructive and solvent action on most bacteria and other organic matter. In the treatment of infected wounds with hypochlorite solutions at present in vogue, the alkalinity is held to be objectionable on the grounds that it causes destruction of tissue and irritation of the skin.



Organic preparations containing a chloramide group which are practically neutral and relatively stable have been proposed as substitutes for hypochlorites on the theory that the action of hypochlorites is dependent on the combination of their active chlorine with the nitrogen of proteins.

### Hypochlorite Preparations

**ANTIFORMIN.**—A strongly alkaline solution of sodium hypochlorite. In each 100 Cc. it contains approximately sodium hypochlorite equivalent to 5.68 Gm. available chlorine sodium hydroxide 7.8 Gm., and sodium carbonate 0.32 Gm.

*Actions and Uses.*—Antiformin rapidly dissolves the bodies of bacteria with the exception of acid-fast organisms like the tubercle bacillus, on which it has no solvent action and which resists its germicidal action to a great extent. It dissolves other organic matters, such as those contained in sputum and feces. It exerts a strong oxidizing action and is disinfectant, antiseptic and deodorizing. It is said to be more than three times as active in germicidal action as phenol.

Because of its property of dissolving most bacteria and the insoluble constituents of the sputum, antiformin is employed in testing for tubercle bacilli. It is said to be useful for the sterilization of the surgeon's hands, of instruments and of wounds and for general purposes of disinfection. It is also said to be useful in certain skin diseases.

*Dosage.*—Externally in from 2 to 10 per cent. solution; in a 4 to 1,000 solution as a spray. As a disinfectant 5 per cent. solutions are used. For the demonstration of tubercle bacilli 15 per cent. solutions are suitable.

Manufactured by the American Antiformin Co., New York. U. S. patent No. 691,671 (Jan. 21, 1902; expires 1919). A process for cleaning beer vats and pipes, said process consisting according to the patent specifications "in subjecting the walls of said vats or pipes to the action of a solution composed of about 1 part of alkaline hypochlorite with about  $\frac{1}{2}$  to 1 part of alkaline hydrate, substantially as specified." U. S. trademark No. 61,693.

According to the patent specification chlorinated lime is dissolved in water at the temperature of 35 C. To this a solution of sodium carbonate is added. After standing the supernatant liquid is decanted and to this sodium hydroxide is added.

Antiformin is a yellowish, clear liquid having the peculiar odor characteristic of hypochlorites.

The percentage of available chlorin, of alkali hydroxide and carbonate may be determined by the methods described in the Reports of the Chemical Laboratory of the American Medical Association, 1910.

**CHLORINE-SODA AMPOULES.**—Composed of a sealed glass tube stated to contain liquid chlorine (over 99 per cent. pure) 4.8 Gm. and a sealed glass tube stated to contain monohydrated sodium carbonate 21.3 Gm. and yielding, when the contents of the tubes are dissolved in 1,000 Cc. of water, a solution similar in composition to Surgical Solution of Chlorinated Soda.

To prepare the solution the contents of the tube of monohydrated sodium carbonate are placed in a bottle having a capacity of about 2,500 Cc. and dissolved in 1,000 Cc. water. The tube containing the liquid chlorine is suspended from a rubber stopper and is inserted into the bottle and the stopper firmly secured. The large bottle (after covering with a cloth) is shaken to break the chlorine tube. The contents of the bottle (without releasing the stopper) are then shaken for two minutes or longer. The solution, freed from particles of glass by decantation or filtration, is then ready for use, or its available chlorine may previously be checked by titration.

*Actions, Uses and Dosage.*—See Surgical Solution of Chlorinated Soda.

Manufactured by Johnson & Johnson, New Brunswick, N. J. U. S. patent applied for. No U. S. trademark.

The finished solution contains from 0.45 to 0.50 per cent. sodium hypochlorite. The available chlorine content is determined by titrating 10 Cc. in the presence of an excess of potassium iodide and acetic acid, with tenth-normal sodium thiosulphate solution. For this titration 12.0 to 13.4 Cc. of tenth-normal sodium thiosulphate solution are required.

To determine if the solution contains an excess of alkali a small quantity of powdered phenolphthalein is mixed by rotation with some of the solution contained in a beaker. No red color should be produced.

**HYCLORITE.**—A solution of chlorinated soda, each 100 Gm. of which is stated to contain sodium hypochlorite 4.05 Gm., sodium chloride 3.20 Gm., calcium hydroxide 0.25 Gm., inert salts 0.92 Gm. It contains not less than 3.85 per cent. available chlorine.

*Actions and Uses.*—Hyclorite has the action and uses of solution of chlorinated soda, U. S. P., but its available chlorine content is greater. One volume of hyclorite diluted with 7 volumes of water has the same available chlorine content as neutral solution of chlorinated soda, and is isotonic.

*Dosage.*—Hyclorite is used full strength or diluted with 1 or 2 parts of water for direct application to mucous membrane, muscular tissue, bone infections, etc. For irrigation of wounds, throat and body cavities dilutions of 1:100 to 1:1,000 are used. For use in the irrigation method of treating infected wounds dilute 1 part of hyclorite with 7 parts of water.

The available chlorine content of hyclorite decreases at the rate of about 12 per cent. per year. In order that due allowance for this decrease may be made when diluting for use, each bottle of hyclorite bears the date of bottling.

Manufactured by the General Laboratories, Madison, Wis. No U. S. patent. U. S. trademark No. 120,110.

Hyclorite is prepared by decomposing chlorinated lime suspended in water with sodium carbonate and adding to the solution obtained, a freshly prepared solution of electrolyzed sodium chloride.

Hyclorite has the properties of solution of chlorinated soda, U. S. P., but contains no carbonate. When exposed to air a pellicle forms on its surface due to the formation of calcium carbonate.

About 10 Gm. hyclorite are weighed and transferred to a dish with about 100 Cc. of water and an excess of pure ammonium hydroxide solution is added. After about one-half hour the solution is evaporated to complete dryness on a water bath. To the residue is added about 50 Cc. of water, 2 drops of methyl orange test solution and an excess (measured) of tenth-normal hydrochloric acid volumetric solution and then the residual acidity determined by titration with tenth-normal sodium hydroxide volumetric solution. The alkalinity found corresponds to not more than 0.25 Gm. calcium hydroxide per 100 Gm. of hyclorite. Each Cc. of tenth-normal hydrochloric acid volumetric solution consumed corresponds to 0.0037 Gm.  $\text{Ca}(\text{OH})_2$ .

Mix in a flask about 5 Cc. of hyclorite, accurately weighed, with 50 Cc. of distilled water, add 1 Gm. of potassium iodide and 5 Cc. of acetic acid and titrate with tenth-normal sodium thiosulphate volumetric solution, starch test solution being used as indicator. It shows not less than 3.85 per cent. available chlorine.

Each Cc. of tenth-normal sodium thiosulphate volumetric solution used corresponds to 0.003546 Gm. of available chlorine. Due allowance should be made for the decrease in available chlorine content of about 12 per cent. per year, date of bottling being stamped on each bottle.

**SURGICAL SOLUTION OF CHLORINATED SODA.**—Solution Chlorinated Soda, Carrel-Dakin.—Solution Chlorinated Soda, Daufresne.—A slightly alkaline chlorinated soda solution containing in 100 Gm. 0.38 to 0.48 Gm. of "available" chlorine; equivalent to 0.4 to 0.5 Gm. sodium hypochlorite ( $\text{NaOCl}$ ).

*Actions and Uses.*—Surgical solution of chlorinated soda is a rapid germicide and efficient antiseptic for infected wounds, when it is used after free incision and cleansing, and applied by practically continuous irrigation, as in the Carrel technic.

Its strength and reaction are carefully adjusted so as to be practically nonirritant to wounds. The skin, however, is subject to irritation and must be protected by petrolatum. The solution does not precipitate proteins, but, on the contrary, dissolves necrotic tissues, and thus helps to keep the wound clean. On the other hand, it dissolves silk ligatures and loosens catgut, thus favoring secondary hemorrhage. The solution is practically nontoxic when used externally. It should not be injected into the peritoneum.

*Dosage.*—For external use, full strength. It is claimed that below 0.4 per cent. of sodium hypochlorite the clinical effect of hypochlorite solutions is *nil*, while above 0.5 per cent. the irritating effect on the skin becomes serious.

Surgical solution of chlorinated soda may be prepared:

1. By the electrolysis of a sodium chloride solution. This method is applicable only where there is suitable apparatus and electric current.

2. By the action of chlorine on sodium carbonate. This may be done either by the use of a specially devised apparatus to measure the chlorine, or by the use of ampules containing a definite weight of chlorine; such ampules are introduced into a container holding a solution of sodium carbonate of the required strength and after the container is tightly stoppered the ampule is broken to permit the chlorine to react with the sodium carbonate.

3. By the interaction of chlorinated lime ("bleaching powder") and sodium carbonate solutions with subsequent treatment with either (a) boric acid or (b) sodium bicarbonate to reduce the alkalinity, as follows:

(a) *Dakin's Method*.—A strong solution of hypochlorite is prepared as follows:

Mix thoroughly 150 Gm. chlorinated lime and 500 Cc. water and to this mixture add 105 Gm. monohydrated sodium carbonate dissolved in 500 Cc. of water. After standing several hours with frequent shaking, the mixture is filtered and a measured portion (20 Cc.) rapidly titrated with half-normal boric acid solution using *powdered* phenolphthalein as an indicator, in order to determine the amount of boric acid to be added to the remainder of the filtrate (each Cc. of half-normal boric acid indicates 3 Gm. of boric acid to be added). It is best to add slightly less than the calculated amount of boric acid. The concentrated solution thus prepared contains about 4 per cent. sodium hypochlorite and may be kept for a month without serious decomposition if protected from light. Before use it should be diluted to its proper strength—usually 1 volume mixed with 7 volumes water—as determined by titration.

(b) *War Demonstration Hospital Modification of Daufresne's Method*.—The per cent. of available chlorine in the chlorinated lime to be employed is first determined.

To make about 40 liters: Place in a 20 liter container the amount of chlorinated lime indicated in the following table; mix this well with 5 liters of tap water and allow to stand several hours.

"Available" Chlorine in Chlorinated Lime, Per Cent.	Chlorinated Lime for 5 Liters Water, Gm.	Monohydrated Sodium Carbonate in 5 Liters Water, Gm.
20-26	800	700
28-34	600	490
36-42	500	390

Dissolve the designated amount of monohydrated sodium carbonate in another 5 liters of water, and pour the solution into the bottle containing the chlorinated lime; mix thoroughly and allow the calcium carbonate to settle. (If all the calcium is not precipitated, add small amounts of sodium carbonate solution until precipitation is complete.) Siphon off the supernatant liquid through a double filter. This concentrated and alkaline solution will keep for several weeks. For use it is treated as follows: A measured portion (20 to 50 Cc.) is titrated with 10 per cent. hydrochloric acid until the red color produced by the addition of solid phenolphthalein disappears (more solid phenolphthalein is added to determine that decolorization was not due to bleaching). The calculated amount of 10 per cent. hydrochloric acid is then added to the original specimen, having a volume designated "V." After the acid has been added a volume the same as "V" of 6.25 per cent. sodium bicarbonate solution is added. The chlorine content of this concentrated solution is now determined by the method prescribed for the assay of solution of chlorinated soda, U. S. P., and it is then diluted to the proper strength.

This solution should meet the following requirements:

If to 20 Cc. of surgical solution of chlorinated soda about 0.02 Gm. of phenolphthalein powder is added, no red color develops on agitation (*absence of excessive alkalinity*).



If to 5 Cc. of the solution contained in a test tube about 0.5 Cc. of 1 per cent. alcoholic solution of phenolphthalein is added ("squirted"), a red color should form and soon disappear (if there is no red flash, the alkalinity is too low).

If the available chlorine of surgical solution of chlorinated soda is determined by the assay method for solution of chlorinated soda, U. S. P., it should contain not less than 0.38 Gm. nor more than 0.48 Gm. available chlorine, in 100 Gm., equivalent to not less than 0.4 Gm. nor more than 0.5 Gm. sodium hypochlorite ( $\text{NaOCl}$ ) in 100 Gm.

### Chloramine Preparations

**CHLORAMINE-B (CALCO).**—Sodium Benzenesulphochloramine.— $\text{C}_6\text{H}_5\text{SO}_2\text{NaNCl} + 2\text{H}_2\text{O}$ .

*Actions and Uses.*—Claimed to be essentially similar to those of chloramine-T (which see).

*Dosage.*—The same as those of chloramine-T (which see).

Manufactured by the Calco Chemical Co., Bound Brook, N. J. No U. S. patent or trademark.

Sodium benzenesulphochloramide was introduced in medicine by Dakin (H. D. Dakin: Brit. M. J., Aug. 25, 1915). It was first made by Chattaway (Trans. Chem. Soc., 87: 153, 1905), by the action of sodium hydroxide on benzenesulphodichloramide. It may also be made by treating benzenesulphonamide with a cold alkaline solution of sodium hypochlorite.

Chloramine-B (Calco) is a white, crystalline powder, having a slight chlorous odor. It may be rendered anhydrous without decomposition by drying.

When a small amount of chloramine-B (Calco) is heated, it melts at 170 to 180 C.

In neutral solutions chloramine-B (Calco) liberates iodine from iodides, but not bromine from bromides; when acidified with hydrochloric acid, the bromine will then be liberated.

Hydrochloric acid added to a solution of chloramine-B (Calco) produces a white turbidity; on heating chlorine is liberated. Chloramine-B (Calco) is decomposed by acids (even boric acid), alcohol and hydrogen peroxide solutions.

If about 0.1 Gm. of chloramine-B (Calco) be treated with a few drops of strong sulphuric acid, chlorine is evolved, but no blackening occurs (*readily carbonizable matter*).

If 0.1 Gm. of chloramine-B (Calco) is dried at 97 to 110 C. in a flat-bottomed dish for two hours, it loses not less than 10 per cent., nor more than 14.4 per cent. of its weight (*water of hydration*).

If about 0.5 Gm. of chloramine-B (Calco) (accurately weighed) is dissolved in 50 Cc. of water, 10 Cc. of potassium iodide solution (10 per cent.), and 5 Cc. of acetic acid (36 per cent.) added and titrated with tenth-normal sodium thiosulphate volumetric solution, the available chlorine should not be higher than 15.0 per cent. or lower than 13.0 per cent. Each Cc. of tenth-normal thiosulphate volumetric solution is equivalent to 0.00177 Gm. of chlorine.

**CHLORAMINE-T.**—Sodium Paratoluenesulphochloramide.  
— $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NaNCl} + 3\text{H}_2\text{O}$ , 1 : 4.

*Actions and Uses.*—The actions of chloramine-T are essentially similar to those of surgical solution of chlorinated soda (which see). It has the advantages of greater stability.

convenience of preparation, and produces less irritation. On the other hand, it lacks the solvent action of alkaline hypochlorites.

It is practically nontoxic, but should not be used by mouth, since it is decomposed by the gastric juice.

**Dosage.**—Chloramine-T is used in 0.1 to 4 per cent. aqueous solution. For wounds, the normal strength is from 1 to 2 per cent., applied by the same technic as the surgical solution of chlorinated soda. It has also been employed for irrigation of the urethra, bladder and uterus, and as a mouth wash.

Sodium paratoluenesulphochloramide was introduced in medicine by Dakin (H. D. Dakin: *Brit. Med. Jour.*, Aug. 25, 1915; H. D. Dakin, J. B. Cohen and J. Kenyon: *Brit. Med. Jour.*, Jan. 29, 1916, p. 160), who proposed the names chloramine (which, however, had been previously applied to the substance  $\text{NH}_2\text{Cl}$ ) and chloramine-T.

Sodium paratoluenesulphochloramide was first made by Chattaway (*Trans. Chem. Soc.*, 1905, lxxxvii, 153) by the action of sodium hydroxide on paratoluenesulphodichloramide. It may also be made by dissolving paratoluenesulphonamide (1 molecule) in a 5 per cent. cold alkaline solution of sodium hypochlorite (1.2 molecule), warming, if necessary, filtering and adding one and one-half volumes saturated sodium chloride solution. The crystals of sodium paratoluenesulphochloramide are collected, washed with sodium chloride solution and dried in the air.

Chloramine-T is a white, crystalline powder, having a slight chlorous odor. It may be rendered anhydrous without decomposition by drying at 100 to 102 C.

Chloramine-T is freely soluble in water, a saturated solution at room temperature containing about 15 per cent. of the salt. One part of chloramine-T dissolves in two parts boiling water. Chloramine-T is insoluble in benzene, ether and chloroform.

When a small amount of chloramine-T is heated, it melts at 160 to 185 C. (with decomposition).

In neutral solutions chloramine-T liberates iodine from iodides, but *not* bromine from bromides; when acidified with hydrochloric acid, the bromine will then be liberated.

Hydrochloric acid added to a solution of chloramine-T produces a white turbidity; on heating chlorine is liberated. Chloramine-T is incompatible with many substances, acids (even boric), alcohol and hydrogen peroxide, for instance.

If about 0.1 Gm. of chloramine-T be treated with a few drops of sulphuric acid, chlorine is evolved but no blackening occurs (*readily carbonizable matter*).

If 1 Gm. of chloramine-T is dried at 100 to 102 C. for two hours, it loses not less than 17 per cent., nor more than 20 per cent. (*water of hydration*).

If about 0.5 Gm. of chloramine-T (accurately weighed) is dissolved in 50 Cc. of water, 10 Cc. of potassium iodid (10 per cent.), and 5 Cc. of acetic acid (36 per cent.) added and titrated with tenth-normal sodium thiosulphate, the chlorine content should not be higher than 13.0 per cent., or lower than 11.5 per cent. Each Cc. of tenth-normal thiosulphate solution is equivalent to 0.00177 Gm. of chlorine.

### Chloramine-T (Calco).—A brand of chloramine-T.

Manufactured by the Calco Chemical Company, Bound Brook, N. J. No U. S. patent or trademark.

**Chloramine-T, Monsanto.**—A brand of chloramine-T.

Manufactured by the Monsanto Chemical Works, St. Louis. No U. S. patent or trademark.

**Chloramine-T, Squibb.**—A brand of chloramine-T.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

*Chloramine-T Surgical Paste-Squibb.*—It contains chloramine-T 1 Gm. in 100 Gm. of a base composed approximately of sodium stearate 15 per cent. and water 85 per cent.

*Chloramine-T Tablets-Squibb, 4.6 grains.*—Each tablet contains chloramine-T 4.6 grains.

**Chlorazene.**—A brand of chloramine-T.

Manufactured by the Abbott Laboratories, Chicago. No U. S. patent. U. S. trademark applied for.

*Chlorazene Surgical Cream.*—It contains chlorazene 1 Gm. in 100 Gm. of a base composed approximately of sodium stearate 15 per cent. and water 85 per cent.

*Chlorazene Tablets, 4.6 grains.*—Each tablet contains chlorazene 4.6 grains.

*Chlorazene Surgical Powder.*—An impalpable powder composed of chlorazene 1 per cent., zinc stearate 10 per cent. and sodium stearate 89 per cent.

**CHLORCOSANE.**—A liquid, chlorinated paraffin containing its chlorine in stable (nonactive) combination.

*Actions and Uses.*—The chlorine of chlorcosane is therapeutically without action. Chlorcosane is used as a solvent for dichloramine-T. With it solutions containing up to 8 per cent. may be prepared. The high viscosity of the oil prevents its being readily sprayed with a hand spray; the addition of about 10 per cent. carbon tetrachloride will reduce the viscosity so that it can be readily sprayed in an ordinary oil atomizer.

Chlorcosane is prepared according to the process of H. D. Dakin and E. K. Dunham (Brit. M. J., Jan. 12, 1918, p. 51): paraffin, having a melting point of 50 C. or higher, is melted and, while the liquid is maintained at a temperature between 125 and 140 C., chlorine is passed in until the weight of the paraffin has increased from 45 to 55 per cent. The resulting liquid, while still warm, is agitated with 5 per cent. of its weight of dry sodium carbonate and filtered.

Chlorcosane is a yellowish to yellowish-brown, oily liquid, odorless, tasteless and neutral to litmus. Its specific gravity is 1 to 1.04 at 15 C.

The chlorine of chlorcosane is not readily removed by treatment with boiling solutions of alkalis and does not react with metallic magnesium suspended in ether. When heated with soda lime to 250 C. unsaturated hydrocarbons and a small proportion of fatty acid are produced. When chlorcosane is boiled with anilin, most of its chlorine is removed.

**Chlorcosane-Abbott.**—A brand of chlorcosane.

Manufactured by the Abbott Laboratories, Chicago. No U. S. patent or trademark.

**Chlorcosane-Calco.**—A brand of chlorcosane containing from 31 to 35 per cent. of chlorine in stable (nonactive) combination.

Manufactured by the Calco Chemical Company, Bound Brook, N. J. No U. S. patent or trademark.

When assayed by the Carius method chlorcosane-Calco contains from 31 to 35 per cent. of chlorine.

**Chlorcosane-Monsanto.**—A brand of chlorcosane containing from 27 to 30 per cent. of chlorine in stable (nonactive) combination.

Manufactured by the Monsanto Chemical Works, St. Louis. No U. S. patent or trademark.

When assayed by the following method chlorcosane-Monsanto contains 27 to 30 per cent. of chlorine:

Mix intimately 10 Gm. of sodium peroxide ( $\text{Na}_2\text{O}_2$ ) and 1 Gm. of sodium nitrate ( $\text{NaNO}_3$ ) and place about one-third of the mixture in a Parr bomb as used in sulphur determinations. Transfer 0.2 to 0.3 Gm. of chlorcosane, accurately weighed (from a narrow neck weighing bottle), into the bomb; cover the sample of chlorcosane with the remaining mixture of peroxide and nitrate. Close the bomb and screw down the cover tightly with the clamp. Heat the bomb rapidly to redness. The fusion is complete when a flash of flame is emitted from the small opening in the cover of the bomb. Cool by allowing tap water to flow over the bottom. Open the bomb and place it in a covered beaker containing 200 c.c. of hot water. After solution is complete, transfer the liquid to another beaker, returning the bomb in the first beaker, washing well with hot water and adding the wash waters to the first liquor. Add nitric acid until the solution reacts acid to litmus paper and heat to boiling. Cool and add an excess of tenth-normal silver nitrate solution; the excess is titrated with ammonium-sulpho-cyanide, ferric ammonium sulphate being used as indicator.

A blank test for chlorine is made on the reagent, using the same amounts and procedures but omitting the chlorcosane. Each Cc. tenth-normal silver nitrate solution used equals 0.003546 Gm. chlorine.

**Chlorcosane-Squibb.**—A brand of chlorcosane.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

**DICHLORAMINE-T.**—Paratoluenesulphonedichloramide.— $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\text{NCl}_2$ .—The dichloramide of paratoluenesulphonic acid,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\text{OH}$ .

*Actions and Uses.*—Dichloramine-T is an effective germicide through its content of active chlorine. It is only sparingly soluble in water, but soluble in chlorinated eucalyptol or chlorinated paraffin oil (chlorcosane). These solutions produce a gradual, sustained antiseptic action.

It is more irritant than chloramine-T, but also more solvent. It should not be administered internally.

Dichloramine-T is claimed to be useful in the prevention and treatment of diseases of the nose and throat; it has been used with success as an application to wounds.

*Dosage.*—Dichloramine-T dissolved in chlorinated eucalyptol-Dakin and chlorinated paraffin oil-Dakin (which see), or



dissolved in chlorcosane (which see), is used in concentrations of 2 to 10 per cent. When used as a spray a 10 per cent. solution of dichloramine-T, in chlorinated eucalyptol-Dakin, is mixed with four times its volume of chlorinated paraffin oil-Dakin. For application to infected wounds a 10 to 15 per cent. solution of dichloramine-T in chlorinated eucalyptol-Dakin, is mixed with from one-half to twice its volume of chlorinated paraffin oil-Dakin. (The solution of dichloramine-T in eucalyptol is fairly stable, but the dilutions of this with chlorinated paraffin oil-Dakin should be prepared freshly when wanted).

Paratoluenesulphonedichloramide was introduced into medicine by H. D. Dakin and co-workers under the name "Dichloramine-T." It is prepared by chlorinating paratoluenesulphoneamide with subsequent purification (J. A. M. A., July 7, 1917, p. 27).

Dichloramine-T is a pale yellowish crystalline powder, having a strong chlorous odor. It melts at 78 to 83 C. It is insoluble in water, soluble in chloroform and benzene, soluble with difficulty in petroleum ether, slightly soluble in liquid petrolatum and soluble in eucalyptol.

Strong mineral acids liberate chlorine from dichloramine-T. It reacts with most substances, such as acids, alcohol, hydrogen peroxide, amines, certain metals, etc. It liberates bromine from bromides and iodine from iodides in neutral solutions.

To 15 Cc. of water add 0.05 Gm. of dichloramine-T and 0.5 Cc. of sodium hydroxide test solution. To this add about 1 Cc. of a saturated solution of aniline. A deep violet color is produced which on dilution becomes blue.

Two Gm. of dichloramine-T are treated with 10 to 15 Cc. of concentrated hydrochloric acid and heated to dryness. The residue is dissolved in a mixture of 1 part alcohol to 1 part water, and an excess of sodium carbonate added. The alcohol is removed by evaporation, and the cooled solution (with considerable insoluble material) is placed in a separating funnel and shaken with chloroform. The chloroform is drawn off, evaporated, the residue dissolved in smallest amount of cold chloroform, and then treated with an excess of petroleum ether. A white precipitate is formed, which, after drying, melts at 134 to 136 C. (pure paratoluenesulphoneamide melts at 137 C.).

If 0.1 Gm. of dichloramine-T is treated with a few drops of sulphuric acid, chlorine is evolved but no blackening occurs (*readily carbonizable matter*).

About 0.1 Gm. of dichloramine-T, accurately weighed, is dissolved in 5 Cc. of glacial acetic acid, 10 Cc. of 10 per cent. aqueous solution of potassium iodide added and the mixture titrated with tenth-normal volumetric sodium thiosulphate solution. (If the reagents used liberate iodine, the number Cc. of tenth-normal sodium thiosulphate volumetric solution required for their decoloration, as determined by a control, should be deducted from the total volume used.) The chlorine content should not be higher than 29.53 per cent. or lower than 28 per cent. Each Cc. of thiosulphate solution is equivalent to 0.00177 Gm. of chlorine.

**Dichloramine-T, Abbott.**—A brand of dichloramine-T.

Manufactured by the Abbott Laboratories, Chicago. No U. S. patent or trademark.

**Dichloramine-T (Calco).**—A brand of dichloramine-T.

Manufactured by the Calco Chemical Company, Bound Brook, N. J. No U. S. patent or trademark.

**Dichloramine-T, Monsanto.**—A brand of dichloramine-T.

Manufactured by the Monsanto Chemical Works, St. Louis. No U. S. patent or trademark.

**Dichloramine-T, Squibb.**—A brand of dichloramine-T.

Manufactured by E. R. Squibb and Sons, New York. No U. S. patent or trademark.

**HALAZONE.**—Parasulphonedichloramidobenzoic acid.— $C_6H_4(SO_2NCl_2)COOH$ -1:4.

**Actions and Uses.**—Halazone is said to be a powerful disinfectant. It is said to act like chlorine, but to have the advantage of being stable in solid form. In the presence of alkali carbonate, borate and phosphate, Dakin and Dunham report that, in from thirty to sixty minutes, halazone in the proportion of 1:200,000 to 1:500,000 sterilized polluted water contaminated with such organisms as the *Bacillus coli*, *Bacillus typhosus*, *Bacillus paratyphosus* A and B, *Cholera vibrio* and *Bacillus dysenteriae*.

**Dosage.**—For the sterilization of water, 0.004 to 0.008 Gm. halazone, in the form of tablets containing sodium carbonate (or sodium borate) and sodium chloride, is added to 1 liter.

Parasulphonedichloramidobenzoic acid was first prepared by H. D. Dakin and E. K. Dunham (Brit. M. J., May 20, 1917, p. 682) under the name "Halazone." It is prepared by oxidizing paratoluene-sulphoneamid to parasulphoneamidobenzoic acid, and chlorinating the latter.

Halazone is a white powder having a strong odor of chlorine. It is slightly soluble in water and chloroform; insoluble in petroleum ether; soluble in glacial acetic acid, benzene, and with formation of the salt in alkali hydroxide solutions. It crystallizes in stout prisms from glacial acetic acid. The melting point of pure halazone is 213 C.

Halazone liberates iodine from a neutral solution of sodium iodide and bromine from a neutral solution of sodium bromide.

If 15 Cc. of a saturated aqueous solution of aniline are treated with 0.05 Gm. of halazone, the solution acquires a brownish-red color, which becomes deep blue upon supersaturation with ammonia water.

If 0.1 Gm. of halazone is treated with a few drops of concentrated sulphuric acid, chlorine is evolved, but no blackening occurs (*readily carbonizable matter*).

About 0.150 Gm. of halazone (or in the case of halazone tablets, 30 tablets), accurately weighed, is dissolved in from 50 to 100 Cc. of water and 10 Cc. of a 10 per cent. sodium hydroxide solution. Fifteen Cc. of a 10 per cent. potassium iodide solution are added, the mix-

ture then acidified with acetic acid and titrated with tenth-normal sodium thiosulphate volumetric solution. (If the reagents used liberate iodine, the number of Cc. of tenth-normal sodium thiosulphate volumetric solution required for their decolorization should be deducted from the total volume used.) The available chlorine content of halazone should not be higher than 26.26 per cent. or lower than 24 per cent. Each Cc. of tenth-normal thiosulphate volumetric solution is equivalent to 0.00177 Gm. of chlorine. The theoretical chlorine content of pure halazone is 26.26 per cent.

**Halazone-Abbott.**—A brand of halazone.

Manufactured by the Abbott Laboratories, Chicago. No U. S. patent or trademark.

*Halazone Tablets-Abbott.*—Each tablet contains halazone-Abbott 0.004 Gm., anhydrous sodium carbonate 0.004 Gm. and sodium chloride enough to make approximately 0.113 Gm.

**Halazone (Calco).**—A brand of halazone.

Manufactured by the Calco Chemical Company, Bound Brook, N. J. No U. S. patent or trademark.

**Halazone-Monsanto.**—A brand of halazone.

Manufactured by the Monsanto Chemical Works, St. Louis. No U. S. patent or trademark.

**Halazone-Squibb.**—A brand of halazone. Sold only in the form of tablets (see below).

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

*Halazone-Squibb Tablets, 1/16 Grain.*—Each tablet contains halazone-Squibb  $\frac{1}{16}$  grain; anhydrous sodium carbonate  $\frac{1}{16}$  grain, and sodium chloride  $1\frac{3}{8}$  grains.

## IODINE COMPOUNDS

Iodine compounds are used partly for their local irritant and antiseptic effects, which are due probably to the action of free iodine contained in the preparations or liberated from them, and partly for their systemic actions. These may be discussed separately under the headings of "Iodine Preparations Containing Free Iodine," "Iodine Dusting Powders," and "Iodine Compounds for Internal Use."

### Iodine Preparations Containing Free Iodine

**IOCAMFEN.**—A liquid obtained by the interaction of iodine 10 parts, phenol 20 parts and camphor 70 parts, containing about 7.25 per cent. free iodine.

*Actions and Uses.*—Iocamfen is said to have the antiseptic and germicidal properties of iodine and also the analgesic,

stimulating and antiphlogistic properties of camphor and phenol.

Iocamfen is used especially in the treatment and dressing of surgical and traumatic wounds, joint injuries, fractures, infected processes, contusions, etc.

*Dosage.*—Iocamfen is applied in small quantities directly to wounds, the skin, cavities, etc., or on tampons or drainage material. It should not be applied to wet surfaces.

Manufactured by Schering and Glatz, Inc., New York. No U. S. patent. U. S. trademark No. 112,934.

*Iocamfen Ampules.*—Each ampule contains iocamfen 20 minims.

Iocamfen is a dark, reddish-brown, viscid liquid, having a camphoraceous odor. Iocamfen is insoluble in water, but soluble in all proportions in alcohol, ether, benzine and liquid petrolatum.

Iocamfen, like free iodine, interacts with fats and waxes, its free iodine entering into combination.

The free iodine content of iocamfen may be determined as follows: About 2 Gm. iocamfen are weighed into a glass-stoppered flask, dissolved in about 25 Cc. chloroform, about 10 Cc. potassium iodide solution (1:10) added and the free iodine determined by titration, under agitation, with tenth-normal sodium thiosulphate solution, using starch as indicator.

### Iodine Dusting-Powders

Dusting-powders containing iodine in various combinations are widely used in the treatment of wounds, granulating surfaces, abscess cavities, etc., whether due to syphilis or tuberculosis or to other infections. The virtue of such preparations was formerly attributed to a germicidal action, but investigators have found such action very slight. The clinical results are now ascribed to a slight antiseptic action of the iodine, to a stimulation of phagocytosis, and to a diminished secretion of the wound which renders it a less favorable culture medium for germs.

Iodoform has been the standard drug of this class. Other insoluble organic iodine compounds have been introduced to replace iodoform, but with limited success. While they avoid the disagreeable odor and the occasional toxic systemic effects, they also lack much of the efficiency.

The following compounds are included in New and Non-official Remedies:

Airol, Bismuth Oxyiodogallate:  $C_6H_2(OH)_3(COOBiI)(OH)$ .

Aristol, Thymol Iodide:  $(C_6H_2.CH_3.C_3H_7.OI)_2$ .

Vioform, Iodochloroxyquinolin:  $C_8H_4N.OH.ICl$ .

**AIROL.**—See Bismuth Compounds.



**THYMOL IODIDE.**—For description see the U. S. Pharmacopeia under *Thymolis Iodidum*.

**Aristol.**—A name applied to thymol iodide, U. S. P.

Manufactured by *Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany* (The Bayer Company Inc., New York). U. S. trademark No. 17,393.

**Thymol Iodide-Merck.**—A brand of thymol iodide, U. S. P. Merck & Co., New York, distributors.

**VIOFORM.** — Iodochloroxyquinolin. — Nioform. —  $C_8H_4N.OH.I.Cl.$  — A substitution compound of anachlor-ortho-hydroxy-quinoline, resulting from the introduction of one atom of iodine.

*Actions and Uses.*—Vioform is used as an odorless substitute for iodoform. Reports indicate about equal bacteriologic efficiency. Local irritation and systemic toxicity are negligible with ordinary doses.

*Dosage.*—As a dusting powder and as an ointment spray, suppository, or in form of gauze.

Manufactured by *Basler Chemische Fabrik, Basle, Switzerland* (C. Bischoff & Co., Inc., New York). German patent No. 117,767.

*Vioform Gauze.*—Gauze impregnated with a solution of 10 Gm. (150 grains) of vioform, 50 Gm. (750 grains) of absolute alcohol, 10 Gm. (150 grains) of sugar, 25 Gm. (375 grains) of glycerin and 500 Gm. ( $1\frac{1}{2}$  pints) of water.

Hydroxy-quinoline is first chlorinated and dissolved in an alkaline solution, which is then treated with a solution of iodine in potassium iodide when a voluminous yellowish-brown precipitate of vioform is produced. This is washed with a solution of sodium thiosulphate to remove free iodine, and then with 1 per cent. hydrochloric acid until the dried residue melts at from 170 to 175 C.

It is a very voluminous, greenish-yellow powder, crystallizing from glacial acetic acid in needles, melting at 177 to 178 C., practically odorless and insoluble in water and slightly soluble in alcohol; it permits sterilization without decomposition; it is about six times as bulky as iodoform.

Vioform contains 41.57 per cent. of iodine; it gives a green coloration with Millon's reagent or when the alcoholic solution is treated with ferric chloride solution. It dissolves with a brown color in concentrated sulphuric acid and the solution evolves iodine on warming. If this solution, after driving off the iodine, be diluted with water, chlorine can be demonstrated by the usual test with silver nitrate. If a solution of vioform in chloroform is shaken with nitric acid, the chloroform acquires a violet red color, and with nitric acid becomes somewhat yellow.

## Iodine Compounds for Internal Use

These are typified by the ordinary iodides. The mechanism of their action is not understood. The most definite results

are seen in the rapid absorption of certain inflammatory exudates and especially of the tertiary lesions of syphilis (gummas); lesions of the bone, skin, brain, or other internal organs, disappear under adequate doses of the drug. Likewise in actinomycosis and sporotrichosis the action of iodine as iodide is almost specific. The iodides are not germicidal.

The effect of iodides in arteriosclerosis and aneurysm is probably limited to the absorption of syphilitic deposits in the vessel wall. The iodides do not directly lower blood-pressure. They increase the amount of iodothyron and may thus have indirect effects on metabolism.

#### COMPLEX IODINE COMPOUNDS

A striking innovation in iodide therapy has been the introduction of compounds of iodine with proteins and fats. The advocates of these organic combinations assert that they are less irritating to the digestive tract and that they are less inclined to set up the disagreeable symptoms of iodism, for instance, coryza and skin eruptions. Experience confirms in a measure the former claim, but the latter is misleading. Iodism is probably a necessary manifestation of the full physiologic activity of the drug, which is required for the treatment of syphilis and other diseases. If, therefore, a preparation fails to elicit these characteristic symptoms, we conclude that the amount of the drug absorbed is insufficient. Clinical observations show that the organic iodides, in the dosage ordinarily employed, are weaker than the metallic forms.

The approximate percentage of iodine in the official iodides and in the organic compounds of iodine listed in New and Nonofficial Remedies is given in the following table.

Ammonium iodide .....	87.5
Iodalbin .....	21.5
Iodocasein .....	18.0
Lipiodine-Ciba .....	41.0
Potassium iodide .....	76.4
Siomine .....	78.5
Sodium iodide .....	84.6
Thymol Iodide, Aristol.....	45.0
Vioform .....	41.57

The following preparations are included in New and Non-official Remedies:

Iodalbin: A compound of iodine and blood albumin.

Iodo-Casein: A compound of iodine with milk casein.

Lipiodine-Ciba: Ethyl diiodobrassidinate.— $C_{21}H_{39}I_2COO$   
( $C_2H_5$ ).

Siomine: Hexamethylenamine tetraiodide.— $(CH_2)_6N_4I_4$ .

## PROTEIN COMPOUNDS

**IODALBIN.**—A compound of iodine and blood albumin, containing approximately 21.5 per cent. of iodine.

*Actions and Uses.*—When administered to animals iodalbin appears to suffer little change in the acid contents of the stomach, but on passing into the intestines it is dissolved by contact with the alkaline secretion and on absorption exerts a physiologic action similar to that of the soluble iodides. It is indicated in the same cases as the soluble iodides.

*Dosage.*—From 0.3 to 0.6 Gm. (5 to 10 grains) repeated according to indications, or until the desired effects are obtained.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

*Iodalbin Capsules, 5 grains.*—Each capsule contains iodalbin 0.3 Gm. (5 grains).

*Iodalbin and Mercuriol Tablets.*—Each tablet contains iodalbin 5 grains and mercuriol 1 grain.

Iodalbin is prepared by treating blood-albumin with a solution of iodine whereby an insoluble precipitate is produced. This precipitate is separated, purified by the removal of free iodine, dried, powdered and assayed.

Iodalbin is a reddish-colored powder, practically tasteless and possessing a peculiar, rather pleasant odor, suggestive of cane syrup or molasses. It is almost insoluble in water, acids, alcohol and other ordinary solvents, but is readily soluble in strong alkaline solutions; more slowly soluble in dilute alkaline solutions. When heated it evolves iodine vapors copiously and is subsequently consumed to an ash, leaving a small amount of residue.

The presence and amount of iodine can be determined by the usual processes for detecting and estimating this element in organic substances.

**IDO-CASEIN.**—Casein-Iodine.—A compound of iodine with milk casein, containing about 18 per cent. of iodine in organic combination.

*Actions and Uses.*—This drug is said to undergo practically no change in the stomach, but to be quickly digested and absorbed in the form of soluble iodides, in the intestines. It is claimed that ido-casein may be used to advantage as a substitute for the inorganic iodides, as it is said to have less disturbing effect on the digestive organs. It is claimed to be excreted more slowly in the beginning than potassium iodide, but the last traces of it are said to be excreted more promptly.

*Dosage.*—From 0.3 to 1.3 Gm. (5 to 20 grains) as indicated.

Manufactured by the H. K. Mulford Co., Philadelphia. No U. S. patent or trademark.

*Iodo-Casein Tablets, 5 grains.*—Each tablet contains iodo-casein 0.3 Gm. ( $2\frac{1}{2}$  grains).

*Iodo-Casein Tablets,  $2\frac{1}{2}$  grains.*—Each tablet contains iodo-casein 0.15 Gm. (5 grains).

Iodo-casein is prepared by treating a solution of casein in sodium carbonate with a solution of iodine and precipitating with acetic acid.

Iodo-casein is a yellowish-brown powder, almost odorless and tasteless, insoluble in water or acid solutions. It is partially dissolved and decomposed by alkalis.

#### NONPROTEIN COMPOUNDS

**LIPOIODINE—"CIBA."**—Ethyl diiodobrassidate  $C_{21}H_{39}I_2$   $COO(C_2H_5)$ , the ethyl ester of diiodobrassic acid  $CH_3.(CH_2)_7.Cl:Cl.(CH_2)_{11}.COOH$ , containing 41 per cent. of iodine.

*Action and Uses.*—Lipoiodine—"Ciba" is absorbed almost completely and a large percentage enters the nervous tissues. The excretion is slower than with inorganic iodides, but more rapid than with other iodized fats. Because of its insolubility in water and its slower absorption, it is claimed that lipoiodine—"Ciba" is less likely to produce gastric irritation than ordinary iodides.

*Dosage.*—Lipoiodine—"Ciba" is supplied in the form of tablets only (see below). One to three, or in acute cases four to six, tablets, each containing 0.3 Gm. of lipoiodine—"Ciba," are administered daily. The tablets should be chewed before swallowing.

Manufactured by the Society of Chemical Industry in Basle, Switzerland (A. Klipstein & Company, New York). U. S. patent No. 1,024,171 (April 23, 1912; expires 1929). U. S. trademark No. 81,554.

*Tablets Lipoiodine—"Ciba", 0.3 Gm.*—Each tablet contains lipoiodine—"Ciba", 0.3 Gm.

Lipoiodine—"Ciba" crystallizes in white, odorless and tasteless needles, melting at 37 C. It is insoluble in water, slightly soluble in alcohol and very soluble in fatty oils, ether and benzene. Lipoiodine—"Ciba" is decomposed by exposure to direct light.

The iodine content of lipoiodine—"Ciba" may be determined by the method of H. Baubigny and G. Chavanne (Comptes rend. de l'Acad. d. Sc., Paris, 136: 1197-99), (Chem. Centralbl. 2: 69, 1903).

**SIOMINE.**—Hexamethylenamine tetraiodide  $(CH_2)_6.N.I_4$ . It contains 78.5 per cent. iodine.

*Actions and Uses.*—Siomine is decomposed in the intestine with formation of hexamethylenamine and iodide, the rate of absorption and excretion being essentially the same as that of inorganic iodides. It therefore produces the effects of ordinary iodides, from which it differs only in that it can be



administered in solid form. The administration of siomine provokes the luetin reaction.

No therapeutic claims are made for the hexamethylenamine component of siomine, this being present only to render the substance insoluble.

While ordinarily the hexamethylenamine content of siomine may be ignored, the drug should be discontinued if any signs of hexamethylenamine intolerance should arise, such as vesical irritation or hematuria.

*Dosage.*—The same as that of potassium iodide; but siomine is administered in solid form.

Manufactured by the Howard-Holt Company, Cedar Rapids, Iowa. Canadian patent No. 166,652. U. S. patent No. 1,226,394 (May 15, 1917; expires 1934). U. S. trademark No. 107,998.

*Siomine Capsules, ¼ grain.*—Each capsule contains siomine ¼ grain and milk sugar 4¾ grains.

*Siomine Capsules, ½ grain.*—Each capsule contains siomine ½ grain and milk sugar 4½ grains.

*Siomine Capsules, 1 grain.*—Each capsule contains siomine 1 grain and milk sugar 4 grains.

*Siomine Capsules, 2 grains.*—Each capsule contains siomine 2 grains and milk sugar 3 grains.

*Siomine Capsules, 5 grains.*—Each capsule contains siomine 5 grains and milk sugar 2 grains.

Hexamethylenamine tetraiodide was described by Herton in 1888, and a process essentially the same as that used for the preparation of siomine is described by Sugiura and Falk (*Biochem. Bull.* 5:18, 1916). Under the name siomine it was first proposed for therapeutic use.

Siomine is prepared by precipitating hexamethylenamine with iodine-potassium iodid solution, and purifying the precipitate.

Siomine is a red powder, having a slight but characteristic odor and taste. When heated to 138 C., it decomposes with violence.

Siomine is slightly soluble in acetone, alcohol, chloroform, carbon disulphide and ether (with partial decomposition). It is almost insoluble in water, but dissolves with decomposition in aqueous solutions of alkali iodides, of sodium thiosulphate and in diluted hydrochloric acid.

If 5 Gm. siomine is heated with 15 Cc. diluted sulphuric acid, first vapors of iodine (recognized by their color and effect on starch paper) are evolved, later formaldehyde is given off (recognized by its odor and the blackening of paper moistened with silver ammonium nitrate test solution). If the siomine-sulphuric acid mixture is heated until colorless and then supersaturated with potassium hydroxide solution, ammonia is evolved (recognized by its odor and effect on red litmus paper).

If a drop of strong sulphuric acid is added to 0.5 Gm. siomine, decomposition occurs with evolution of brown fumes.

If siomine is incinerated, not more than 0.03 per cent. of ash remains.

If 0.5 Gm. siomine is warmed with 0.5 Cc. hydrochloric acid and 5 Cc. water until a clear solution results, a few drops of barium chloride test solution should not produce a precipitate (*sulphates*).

## IPECAC PRINCIPLES AND PREPARATIONS

**EMETINE BISMUTH IODIDE.**—*Emetinae Bismuthio-Iodidum.*—*Emetine Bismuthous Iodide.*—*Bismuth Emetine Iodide.*—A complex iodide of emetine and bismuth, containing from 17 to 23 per cent. of anhydrous emetine and from 15 to 20 per cent. of bismuth.

*Actions and Uses.*—Emetine bismuth iodide has the action of emetine, but when taken by the mouth, on account of its insolubility, it is less likely to cause vomiting than the soluble salts of emetine administered orally.

It has been used with apparent good results in the treatment of chronic cases and carriers of amebic dysentery, even where the hypodermic administration of emetine had failed.

*Dosage.*—The commonly used dose has been 0.2 Gm. (3 grains) daily for four days, either in a single dose at the midday meal or in divided doses. The drug should be given as dry powder, enclosed in capsules or cachets as desired, or in the form of pills or capsules which resist disintegration in the stomach.

Emetine bismuth iodide is an odorless, orange-red powder having a slightly bitter taste.

It is but slightly soluble (with decomposition and liberation of emetine) in water, and dilute acids. It is decomposed by alkaline liquids and by strong acids.

Shake 0.1 Gm. of emetine bismuth iodide with 10 Cc. of tenth-normal hydrochloric acid volumetric solution during fifteen minutes. Filter and dilute 1 Cc. of the filtrate to 100 Cc. To a 5 Cc. portion add 1 drop of mercuric potassium iodide test solution, shake and allow to stand one minute. No distinct milkeness or turbidity should appear.

When assayed by the following method, emetine bismuth iodide contains from 17 to 23 per cent. of anhydrous emetine and from 15 to 20 per cent. of bismuth.

To about 0.5 Gm., accurately weighed, of emetine bismuth iodide in a glass stoppered flask add 10 Cc. of water and 3 Cc. of ammonia water, shake and allow to stand ten minutes. Add 50 Cc. of ether to the flask, shake for ten minutes and then shake every ten minutes during two hours. Decant 25 Cc. of the ethereal layer into a 25 Cc. graduated flask. Filter this through a pledget of cotton into a small beaker. Wash the flask and filter with ether. Allow the ether to evaporate spontaneously and dry over sulphuric acid. Take up the alkaloid with fiftieth-normal sulphuric acid volumetric solution and titrate back with fiftieth-normal sodium hydroxide volumetric solution using cochineal as an indicator. Each Cc. of fiftieth-normal sulphuric acid volumetric solution consumed is equivalent to 0.0048 Gm. of anhydrous emetine.

Place the flask, containing the residue from the emetine determination, upon the water bath and allow the remaining ether to evaporate. Transfer the aqueous liquid and precipitate to a beaker rinsing the flask with a few Cc. of concentrated hydrochloric acid. Add about 30 Cc. of concentrated hydrochloric acid to the beaker and boil. Dilute to about 300 Cc., again heat to boiling and filter. Add ammonia water until a slight turbidity appears. Add hydrochloric acid drop by drop until the solution just becomes clear. Heat to boiling, add 50 Cc. of 10 per cent. ammonium phosphate solution and boil for several minutes. Let stand for one-half hour. Transfer the precipitate to a tared Gooch crucible, which has been strongly heated for

one hour in a nickel crucible before being weighed. Wash with hot water, dry, and heat in a nickel crucible to constant weight. Each Gm. of bismuth phosphate ( $\text{BiPO}_4$ ) corresponds to 0.6863 Gm. of bismuth.

**Emetine Bismuth Iodide-Abbott.**—A brand of emetine bismuth iodide complying with the New and Nonofficial Remedies standards.

The Abbott Laboratories, Chicago. No U. S. patent or trademark.

**Bismuth Emetine Iodide-Mulford.**—A brand of emetine bismuth iodide complying with the New and Nonofficial Remedies standards.

The H. K. Mulford Co., Philadelphia. No U. S. patent or trademark.

*Cachets Bismuth Emetine Iodide-Mulford, 2 grains.*—Each cachet contains bismuth emetine iodide-Mulford 0.13 Gm. (2 grains).

**EMETINE HYDROCHLORIDE.**—For description see the U. S. Pharmacopeia under *Emetinae Hydrochloridum*.

*Actions and Uses.*—Emetine acts similarly to ipecac. In amebic dysentery, it has various advantages over the oral administration of ipecac, in that its absorption and effects are more rapid and certain, and the gastrointestinal irritation much less. Excessive doses are dangerous, however, and the toxicity seems to vary. Intravenous injections should be avoided.

Emetine has been employed both locally and systemically in pyorrhea alveolaris; but its value in this use has not been definitely established.

*Dosage.*—Expectorant, from 0.005 to 0.01 Gm. ( $\frac{1}{12}$  to  $\frac{1}{6}$  grain). From 0.01 to 0.02 Gm. ( $\frac{1}{6}$  to  $\frac{1}{3}$  grain) causes emesis, but cephaeline is preferred as an emetic. By hypodermic injection, 0.03 Gm. ( $\frac{1}{2}$  grain).

*Ampuls Emetine Hydrochloride-Mulford, 1/12 grain.*—Each ampule contains emetine hydrochloride 0.005 Gm. ( $\frac{1}{12}$  grain). Prepared by H. K. Mulford Co., Philadelphia.

*Ampuls Emetine Hydrochloride-Mulford, 1/3 grain.*—Each ampule contains emetine hydrochloride 0.02 Gm. ( $\frac{1}{3}$  grain). Prepared by H. K. Mulford Co., Philadelphia.

*Ampuls Emetine Hydrochloride-Mulford, 2/3 grain.*—Each ampule contains emetine hydrochloride 0.04 Gm. ( $\frac{2}{3}$  grain). Prepared by H. K. Mulford Co., Philadelphia.

*Ampuls Emetine Hydrochloride-Mulford, 1/2 grain.*—Each ampule contains emetine hydrochloride 0.03 Gm. ( $\frac{1}{2}$  grain). Prepared by the H. K. Mulford Co., Philadelphia.

*Ampuls Emetine Hydrochloride-P. D. & Co.*—Each ampule contains emetine hydrochloride 0.02 Gm. ( $\frac{1}{3}$  grain). Prepared by Parke, Davis and Co., Detroit.

*Friable Tablets of Emetine Hydrochloride-Mulford.*—Each tablet contains emetine hydrochloride 0.03 Gm. Prepared by H. K. Mulford Co., Philadelphia.

*Hypodermic Tablets of Emetine Hydrochloride-Mulford.*—Each tablet contains emetine hydrochloride, 0.016 Gm. Prepared by H. K. Mulford Co., Philadelphia.

**Emetine Hydrochloride-Merck.**—A nonproprietary brand complying with the standards for emetine hydrochloride.

Merck & Co., New York, distributors.

## IRON AND IRON COMPOUNDS

Iron is used in medicine: (1) in the form of metallic or elementary iron (reduced iron, U. S. P.); (2) in the ferrous or unoxidized form of combination—responding to tests for ferrous ions (ferrous carbonate in mass of ferrous carbonate and pill of ferrous carbonate, ferrous iodide in syrup of ferrous iodide, U. S. P.); (3) in the trivalent or oxidized form, the ferric compounds—responding to tests for ferric ions (ferric chloride in tincture of ferric chloride, U. S. P.); and (4) complex compounds of iron.

Complex (masked or non-ionic) iron compounds are those compounds of iron whose solutions do not respond to the ordinary tests for ferrous or ferric ions because in them the iron is part of a radical. Complex compounds of iron do not have the astringent taste of simple iron solutions. The permanence of these complex radicals differs widely; while some are converted to simple ionic iron by action of dilute acids (soluble ferric phosphate, U. S. P., syrup of citro-iodide of iron, N.F., etc.), others resist treatment with strong acids or with alkalis. The complex iron compounds occurring naturally in animal and vegetable tissues (which are often termed food irons) belong generally to the more resistant class, while the complex iron compounds produced artificially are as a rule decomposed rather readily. There is, however, no sharp line of distinction between the natural complex iron compounds and the artificially produced ones, nor is there any good evidence that they differ in therapeutic action. Until a difference in their effects has been demonstrated, we may class together all complex iron compounds whose solutions are not decomposed into simple ionic iron by digestion at body temperature with 0.2 per cent. hydrochloric acid and pepsin. (It should be emphasized that salts of iron which give the iron test directly are classed as inorganic iron, whatever their acid radicals may be, and that true iron albuminate and iron peptonate are inorganic iron compounds.)

*Actions and Uses.*—Solutions of ferric iron are used externally as styptics. Ferric solutions may be used for their astringent effects, internally, and as a gargle. The principal use of iron, however, is in the treatment of anemia and chlorosis. For this purpose the ferrous salts are usually preferred to the ferric salts, as they are not so caustic and hence are less likely to disturb the stomach. Reduced iron, yielding ferrous chloride when dissolved in the stomach, acts as a ferrous compound, provided that the hydrochloric acid in the gastric fluid is sufficient to permit solution. So far as



the complex iron compounds are not decomposed by gastric digestion, they also are devoid of gastric effects; but, on the other hand, it has been claimed that certain hemoglobin-like compounds escape absorption altogether. Bunge supposed that only "organic iron" could be absorbed and assimilated by the body, the reputed action of inorganic iron being altogether indirect and due to its local effect on the alimentary canal. This theory was modified by Abderhalden to the effect that inorganic iron, while it could not be converted into hemoglobin, nevertheless stimulated the conversion of "organic iron." Later work, however (Tartakowski), seems to prove conclusively that inorganic iron is assimilated and converted into hemoglobin and in so far is therapeutically fully equal to natural complex iron compounds. Many authors and practitioners, nevertheless, still adhere to the theories of Bunge and Abderhalden. At all events, a real difference exists between the "organic" and most inorganic preparations in their local irritant and astringent action, which is absent in most of the complex iron compounds. These local actions may be desirable in some cases and undesirable in others. This should mainly determine the selection of the particular iron preparation most suitable for each individual patient. It should also be remembered that "masked" iron can often be administered in sufficient amounts and most economically by selecting a dietary rich in iron, such as red meat, egg-yolk, green vegetables, whole wheat, etc.

### Iron Salts, Simple

**FERRIC CACODYLATE.**—See Arsenic and Arsenic Compounds (Arsenic Compounds, Complex—Organic—Cacodylates).

**FERROUS LACTATE.**—*Ferri Lactas.*—Iron Lactate.—*Ferrum Lacticum.*— $\text{Fe}(\text{C}_3\text{H}_5\text{O}_3)_2 + 3\text{H}_2\text{O}$ .—The ferrous salt of lactic acid. The salt contains approximately 19 per cent. of metallic iron.

*Actions and Uses.*—Ferrous lactate is a mild chalybeate which, because of its feeble taste, may be taken without difficulty.

*Dosage.*—From 0.06 to 1.3 Gm. (1 to 20 grains). Owing to its liability to oxidation, it is best prescribed in solutions containing much sugar. Syrup dissolves 1 Gm. in 120 Gm. (4 grains to the fluidounce).

Ferrous lactate occurs in pale greenish-white crusts, consisting of small needle-shaped crystals or transparent green scales, having a slight, peculiar odor and a sweetish, ferruginous taste. It is slowly soluble in about 40 parts of cold and in 12 parts of boiling water; almost insoluble in alcohol; freely soluble in a solution of an alkali.

citrate, yielding a green solution. When strongly heated the salt froths, gives out dense, white, acid fumes, chars and finally leaves a brownish-red residue.

The aqueous solution of the salt has a greenish-yellow color, a slightly acid reaction, and gives a deep blue precipitate with potassium ferricyanide, and a light blue one with potassium ferrocyanide. A 2 per cent. aqueous solution of the salt should not yield more than a faint opalescence with a solution of lead acetate (*limit or absence of sulphate, chloride, citrate, tartrate and malate*). The aqueous solution after acidulation with hydrochloric acid should not yield any precipitate or coloration when treated with hydrogen sulphide (*foreign metals*). The aqueous solution, acidulated with nitric acid, should not afford more than a slight opalescence with barium chloride solution or with silver nitrate solution (*limit of sulphate or chloride*). If 25 Cc. of a 2 per cent. aqueous solution of the salt be mixed with 5 Cc. of diluted sulphuric acid, the mixture boiled for a few minutes, an excess of sodium hydroxide added and the mixture filtered, the filtrate, when mixed with a few drops of alkaline cupric tartrate solution and boiled, should not yield a red precipitate (*sugar*). If a portion of the salt be triturated with strong sulphuric acid no offensive odor should be developed (*butyric acid*), nor should any gas be evolved (*carbonate*), and the mixture, after standing for some time, should not assume a brown color (*sugar, gum or other readily carbonizable impurities*). If 1 to 1.5 Gm. of the salt be weighed and moistened with nitric acid and carefully ignited in a porcelain crucible it should leave a residue of ferric oxide, weighing not less than 27 per cent. nor more than 27.8 per cent. of the material taken. This residue should not have an alkaline reaction on litmus paper, nor yield anything soluble to water (*foreign salts*).

**Iron Lactate-Merck.**—A nonproprietary brand complying with the standards for ferrous lactate.

Merck & Co., New York, distributors.

### Iron Salts, Complex

**ARSENOTRIFERRIN.**—See Arsenic Compounds.

**BISMUTH AND IRON CITRATE (Soluble) Wellcome Brand.**—See Bismuth Compounds.

**FERRO-MANGAN-Dieterich, — Liquor Ferro-Mangani Peptonati—"Dieterich."**—A solution of a compound of peptone with iron and manganese, containing 0.6 per cent. of iron, 0.1 per cent. of manganese and 1.5 per cent. of peptone.

**Actions and Uses.**—Ferro-mangan has the actions of iron and manganese.

It is said to be useful in anemia, chlorosis, convalescence and as a general tonic.

**Dosage.**—From 4 to 16 Cc. (1 to 4 fluidrachms), according to age, three times a day.

Manufactured by Chemische Fabrik Helfenberg A. G., near Dresden, Germany (The Reinschild Chemical Co., New York). No U. S. patent or trademark.

Ferro-mangan is prepared by covering 40 Gm. of iron and manganese peptonate "Dieterich" with distilled water for one hour, then heating to boiling with 550 Cc. of distilled water and allowing to cool. An aromatic mixture is added consisting of 100 Cc. cognac, 75 Cc. alcohol, 90 per cent., 0.25 Gm. saccharin, 12.5 Cc. aromatic tincture, and sufficient distilled water to make 1,000 Cc.

Ferro-mangan is a clear liquid of a dark-brown color and a pleasant odor and taste. It is slightly acid in reaction. The iron is in the organic or non-ionic form (see preceding general article, Iron and Iron Compounds). Ferro-mangan should have a specific gravity of about 1.056 at 15 C. When dried at 100 C. the residue varies between 13.25 and 16.80 per cent. When ignited ferro-mangan leaves a residue weighing 0.99 to 1.05 per cent. of the material taken. Ferro-mangan should contain from 0.58 to 0.64 per cent. of iron and from 0.13 to 0.19 per cent. of manganese.

**OVOFERRIN.**—A solution containing 5 per cent. of an artificial protein product in which iron is present in the so-called "organic" or "masked" form (a form which does not give the iron test directly) equivalent to 0.4 Gm. metallic iron to each 100 Cc. The solution also contains 9 per cent. of alcohol.

*Actions and Uses.*—Ovoferrin is stated to be not appreciably affected by the gastric juice, 0.5 per cent. solution of hydrochloric acid liberating its iron very slowly and incompletely. The product ranks with the other forms of artificially masked iron, which are devoid of the local action of the soluble inorganic iron salts, and, according to some authorities, are more readily absorbed and utilized.

*Dosage.*—From 8 to 15 Cc. (2 to 4 fluidrachms) corresponding to from 0.03 to 0.06 Gm. ( $\frac{1}{2}$  to 1 grain) of elemental iron three times a day.

Manufactured by A. C. Barnes Co., Philadelphia. U. S. trademark.

Ovoferrin is prepared by modifying serum albumin by electrolysis and introducing ferric hydroxide into this modified protein by heating under pressure.

The solution has a reddish-brown color, little odor, and a flat, slightly aromatic and alcoholic taste.

Ovoferrin does not give a blue color on the addition of potassium ferrocyanide solution; a blue tint develops slowly if an equal volume of 5 per cent. hydrochloric acid is added to the mixture; a deep blue color develops at once if this mixture is boiled (difference from the egg-yolk). The solution is not precipitated by boiling, but gives precipitates with the alkalis, with which it is incompatible. It is also precipitated on half saturation with ammonium sulphate. It is not precipitated by acids.

**PROFERRIN.**—Iron Nucleo-Proteid.—A compound of iron and milk casein containing iron equivalent to about 10 per cent. elementary iron, and phosphorous equivalent to about 0.5 per cent. elementary phosphorus.

*Actions and Uses.*—Proferrin has been recommended as a ferruginous tonic and as a means of restoring the iron and

phosphorus waste of the body. It undergoes very little change in the stomach, but is said to be quickly digested and absorbed in the intestine. Its hematogenous actions resemble those of other organic iron preparations.

*Dosage.*—0.13 to 0.3 Gm. (2 to 5 grains).

Manufactured by the H. K. Mulford Co., Philadelphia. No U. S. patent. U. S. trademark No. 38,614.

*Proferrin Tablets, 1 grain.*—Each tablet contains proferrin 0.065 Gm. (1 grain).

*Proferrin Tablets, 2 1/2 grains.*—Each tablet contains proferrin 0.15 Gm. (2½ grains).

*Proferrin Tablets, 5 grains.*—Each tablet contains proferrin 0.3 Gm. (5 grains).

Proferrin is prepared by treating an alkaline solution of casein with a solution of an iron salt and precipitating with acetic acid. Proferrin is a brown powder, almost odorless and tasteless, insoluble in water and dilute acids, slowly soluble in alkalis.

If, to the dry powder, fuming nitric acid be added, an orange red color, due to the protein, results. If the dry powder be heated in a crucible, the odor of burning nitrogenous matter will be given off, and the residue, if dissolved in hydrochloric acid, will give the usual tests for iron. If 0.5 Gm. be shaken with 10 Cc. distilled water, and the mixture filtered, the filtrate should give no precipitate on addition of ammonium hydroxide, and not more than a faint bluish tint on addition of a few drops of potassium ferrocyanide solution (limit of *inorganic iron*). If about 2 Gm. proferrin be digested for three hours at 40 C., with 40 Cc. of 0.2 per cent. hydrochloric acid containing 0.006 Gm. pepsin, U. S. P., and the resulting mixture filtered, 5 Cc. of the filtrate diluted to 100 Cc. should produce not more than a faint blue color on the addition of a drop of potassium ferrocyanide solution. The iron and phosphorus may be determined by the usual methods for organic compounds containing these elements.

**TRIFERRIN.**—Triferrinum.—Ferric Paranucleinate.—A compound of caseinparanucleinic acid with iron, containing 22 per cent. of iron, 9 per cent. of nitrogen and 2.5 per cent. of phosphorus in natural (organic) combination.

*Actions and Uses.*—In addition to its hematinic action derived from the iron, triferrin is claimed to act like lecithin by reason of the phosphorus in organic combination which it contains. It is said to agree with very sensitive stomachs, since it passes the stomach unchanged, but is freely absorbed in the intestines.

It is said to be useful in anemia, chlorosis, neurasthenia, rachitis and general debility.

*Dosage.*—0.3 Gm. (5 grains) in powder, taken during meals.

Manufactured by Knoll & Co., Ludwigshafen a/Rh., Germany, and New York (E. Bilhuber, New York, distributor). German patent No. 114,273. U. S. trademark No. 36,747.

*Triferrin Tablets, 5 grains.*—Each tablet contains triferrin, 5 grains.

*Triferrol.*—Liquor Triferrini, Knoll.—Triferrol is an elixir of triferrin, said to contain 0.06 Gm. (1 grain) triferrin in 4 Cc. (1 fluidrachm). It contains 15 per cent. of alcohol.



A soluble form of triferrin (soluble triferrin Knoll) is dissolved in a vehicle consisting of water, alcohol, tincture of orange, compound tincture of cardamom and vanillin.

*Dosage.*—16 Cc. (4 fluidrachms) corresponding to 0.24 Gm. (4 grains) of the powder.

Triferrin is prepared by digesting cow's milk casein with pepsin and precipitating the solution with a ferric salt.

It is a tasteless powder. It is soluble in weak solution of sodium hydroxide, but insoluble in weak hydrochloric acid (from 0.1 to 0.3 per cent.).

### Iron Salts, Complex—Hemoglobin Derivatives

Hemoglobin is the coloring matter of the blood-corpuscles and is the most important iron-containing compound of the body. It exists in venous blood as hemoglobin, sometimes called reduced hemoglobin, and in the lungs takes on oxygen in a loose chemical combination becoming oxyhemoglobin.

Hemoglobin is obtained from oxyhemoglobin by the action of various reducing agents.

When ingested it is decomposed in the stomach, being converted into a protein, globin, and into hematin, an acid, non-albuminous substance, containing the iron of hemoglobin. The same decomposition is produced by heating in solution to 70 C., and by various chemical agents. It is doubtful whether hemoglobin is absorbed into the blood from the gastro-intestinal canal.

Various preparations of hemoglobin have been put on the market. These are of two classes. 1. Preparations consisting essentially of oxyhemoglobin, usually sold under the name "hemoglobin." 2. Preparations derived by the action of reducing agents on the blood, such as zinc, pyrogallol, etc. They consist of reduced hemoglobin or of some modification of it.

### LACTIC ACID-PRODUCING ORGANISMS AND PREPARATIONS

According to the theories of Metchnikoff the products of intestinal putrefaction are the cause of a condition of chronic poisoning, autointoxication, which, chiefly through action on the walls of the blood vessels, brings about arteriosclerosis and premature senility. These putrefactive products result from the growth of proteolytic organisms, many of them anaerobic in character. According to Metchnikoff the growth of these pathogenic bacteria is modified or prevented by the presence in the intestinal tract of lactic acid-producing bacteria, particularly of *Bacillus bulgaricus*. While the theories of Metchnikoff have many supporters, in general they lack scientific proof, and by some competent investigators the practicability of modifying the intestinal flora by implantation of *Bacillus bulgaricus* is denied. On the other hand, there is much evidence that the administration of sour milk products is at times beneficial. Conservative physicians

believe that in certain conditions, substitution of sour milk in place of protein food produces improved nutrition, and to a certain extent inhibits putrefaction. Others who are more enthusiastic are inclined to attribute to this treatment a wide range of therapeutic effects on insufficient evidence, while others, particularly interested parties, have asserted that the ingestion of certain sour milk preparations will cure anything from "stomach trouble" to gallstones, locomotor ataxia and tuberculosis. The Council believes that in certain conditions the ingestion of sour milk preparations is of established value, but that the administration of cultures of *Bacillus bulgaricus* with a view of securing their growth in the intestines is of doubtful utility.

There is some evidence to indicate that liquid cultures of lactic-acid-producing organisms may be of service in arresting putrefaction in wounds, abscesses and in the various body cavities and to be beneficial in chronic suppurative processes of the nasal passages and the accessory sinuses of the middle ear, the endometrium and the vagina.

The use of lactic acid preparations may be divided into (1) administration of milk soured by addition of bacteria, (2) administration of the bacteria themselves and (3) application of cultures of these bacteria to sinuses, nasal cavities, etc.

Sour or fermented milk may be administered in the form of buttermilk or soured skimmed milk, the lactic acid being produced by action of the paralactic acid bacillus *Streptococcus lacticus*, which grows readily at room temperature, or in the form of sour milk produced by the Bulgarian bacillus, *Bacillus bulgaricus*, alone or in presence of *Streptococcus lacticus*. An objection to the use of the Bulgarian bacillus is that the fermentation must be carried out at a temperature of 45 C. or higher and that the product is not very palatable. Metchnikoff therefore recommended association of the two bacilli named. Kefir and koumiss are produced by the action of lactic acid-producing organisms associated with an alcohol-producing yeast, which also acts on the proteins of milk and renders them somewhat more digestible. The alcohol content makes caution in their use by children and invalids advisable.

When the ferments are administered in the attempt to cause their implantation in the intestinal tract, the Bulgarian bacillus is commonly, though without good reason, given preference, either in the form of tablets or of liquid cultures. For application to sinuses, nasal cavities, etc., pure cultures in aqueous suspension are generally used.

*Bacillus bulgaricus* or *B. lactis bulgaricus* belongs to a group of bacteria which has not received much scientific attention. This group of bacteria is widely distributed through nature, but has been generally overlooked, because the common laboratory mediums are wholly unsuitable for their growth. The bacteria of this group answer to the following characteristics: *Bacillus bulgaricus* is a long bacillus, sometimes

fairly slender and sometimes fairly thick. It has a tendency to filament formation in old cultures. It grows preferably under anaerobic conditions, but grows well also under aerobic conditions. Different strains vary in this respect. Young cultures are gram-positive, but in old cultures many gram-negative forms appear. If the gram stain is applied and a red counterstain used, one filament may appear blue in some parts and red in others. Sometimes there is a tendency to granular staining if methylene blue is used. Branching has been frequently observed, the bacillus taking on the shape of the letter "Y."

Carbohydrates are essential to successful cultivation of this bacillus. Broth with 2 per cent. dextrose is quite suitable for most strains, especially if calcium carbonate in the form of pieces of marble is added, so that the acid formed during growth is promptly neutralized. Some strains are said to grow well on beerwort. The medium par excellence is milk or some medium prepared from milk. Milk agar, prepared by precipitating the casein and dissolving agar in the whey, is an excellent medium if dextrose is added. Milk is acidified rapidly and a coagulum is formed with little separation of whey. The amount of acid formed varies with different strains from 1 to 3 per cent. or even more.

Two varieties of *B. bulgaricus* are used for the preparation of a milk which is usually called Bulgarian milk. One of these strains forms a slimy milk; the other does not. The slime-forming strain usually separates no whey. The other variety usually separates a small amount of whey. The coagulum is smooth and flows like thick cream. The slime-forming property may be lost temporarily or permanently. By frequent transfers on milk the slime-forming property is preserved and even enhanced. Old cultures are not slimy. Under what conditions slime-forming properties are acquired is not known.

The acid produced is 94 per cent. lactic acid. It has been stated that the butter fat and the casein are decomposed. If this is true the reaction is slow and the result not noticeable for several days.

The group of bacilli to which *B. bulgaricus* belongs is sometimes called "lactobacilli." They are able to multiply in the presence of considerable amount of acid and therefore belong to the group often misnamed as acidophil. They are not acidophil in the true sense of the word, but are acid-resisting. Whether we are justified in distinguishing species in this group, or only varieties, remains a subject for research. Probably the lactobacilli form a large group consisting of many varieties, similar to the *B. coli* group or the group of streptococci. Research will probably show that some varieties retain their properties with tenacity, while other varieties are readily transformed.

Market milk usually contains bacilli of this group. The optimum temperature for cultivation is about 45 C. Milk incubated at this temperature will, as a rule, turn very sour in the course of several days and show an acidity of from 2 to 3 per cent. The lactobacilli have been considered active in the ripening of certain cheeses. They are found frequently in feces of man and animals. It is stated that the feces of infants can be used for the preparation of buttermilk after several transfers through milk. The Bulgarians, if they lose their "maya," which is the name of the starter for their sour milk, can replace it by using part of the stomach or intestines of a calf.

Cultures may be prepared in broth containing dextrose, or, better, in sterilized milk. Viability decreases rapidly. Frequent transfers are therefore necessary. To preserve a culture in best condition it should be transferred at least once every two days. A milk culture will contain living bacilli for many days, but their activity becomes impaired and the slime-producing property is lost. The amount of acid formed also becomes less.

**B. B. CULTURE.**—A pure culture of *Bacillus bulgaricus* said to be made from a desirable strain; marketed in bottles containing about 90 Cc. (3 fluidounces).

*Actions and Uses.*—B. B. culture is adapted both for internal and external use. See preceding general article, Lactic Acid-Producing Organisms and Preparations.

*Dosage.*—From 4 to 8 Cc. (from 1 to 2 fluidrachms) three times a day in sweetened water before meals. For babies of any age 1 teaspoonful every three hours. The date of issue is stated on each bottle.

Manufactured by the B. B. Culture Laboratory, Yonkers, N. Y. No U. S. patent. U. S. trademark No. 90,535.

**BACILLARY MILK.**—A sterilized fat-free milk fermented by the action of a pure culture of *Bacillus bulgaricus* and containing over 2 per cent. of lactic acid.

*Actions and Uses.*—Bacillary milk is used as a means for the administration of the Bulgarian bacillus and for its lactic acid as well as for its nutritive value. See preceding general article, Lactic Acid-Producing Organisms and Preparations.

*Dosage.*—When the acidity is distasteful the portion of the milk directed to be taken may be rendered palatable by mixture with milk or water or by addition of sugar. Bacillary milk is put up in glass bottles, each containing 1 pint, and should be kept on ice.

Because of limited keeping qualities, this product is not generally carried in stock by druggists, but may be obtained direct from the manufacturer.

Manufactured by Fairchild Bros. & Foster, New York. No U. S. patent or trademark.

Bacillary milk is said to contain the Bulgarian bacilli in pure culture. It has the marked acidity characteristic of milk soured by *Bacillus bulgaricus* and is free from sliminess or bitterness. It is said that in a cold place it may be kept for a long time without impairment of its qualities.

**BULGARA TABLETS.**—H. W. & D.—Tablets containing a practically pure culture of *Bacillus bulgaricus*.

*Actions and Uses.*—See preceding general article, Lactic Acid-Producing Organisms and Preparations.

*Dosage.*—One or two tablets before or after meals. The diet should contain a sufficiency of sugar.

Bulgara tablets are marketed in tubes, each containing 50 tablets, with an expiring date stamped on the label.

Manufactured by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.



Bulgara tablets consist of the slowly dried cultures mixed with milk sugar and starch, each tablet weighing 5 grains and containing a sufficient number of viable organisms to effect the souring of a pint of sterile milk in less than twenty hours.

**BULGARIAN BACILLUS TABLETS-MULFORD.**—Tablets containing a practically pure culture of *Bacillus bulgaricus*.

*Actions and Uses.*—See preceding general article, Lactic Acid-Producing Organisms and Preparations.

*Dosage.*—For adults and children, 1 or 2 tablets after meals and at bed time. For infants, 1 or 2 tablets with each feeding. The tablets are marketed in vials of 50 tablets. An expiration date is stamped on the label.

Manufactured by the H. K. Mulford Co., Philadelphia. No U. S. patent or trademark.

A culture of *Bacillus bulgaricus* grown on whey is mixed with starch, sugar and milk sugar, dried and compressed into tablets.

**CULTURE OF BACILLUS BULGARICUS - FAIRCHILD.**—A pure culture in vials of *Bacillus bulgaricus*, each vial containing about 7 Cc.

*Actions and Uses.*—The Fairchild culture of *Bacillus bulgaricus* is designed for internal administration and for direct application to body cavities, abscesses and wounds. See preceding general article, Lactic Acid-Producing Organisms and Preparations.

*Dosage.*—Internally, the contents of one vial is the usual daily dosage. The culture is supplied in boxes of six and in boxes of thirty vials. The vials must be kept in a cold place and are not guaranteed beyond the date stamped on the package.

Manufactured by Fairchild Bros. & Foster, New York. No U. S. patent or trademark.

The bacilli are obtained by inoculation and incubation on Cohendy peptone-sugar-broth medium.

**CULTURE OF THE BACILLUS BULGARICUS-LEDERLE.**—A pure culture in vials of *Bacillus bulgaricus*, each vial containing about 5 Cc.

*Actions and Uses.*—The culture of *Bacillus bulgaricus*-Lederle is designed for internal administration and for direct application to body cavities, abscesses and wounds. See preceding general article, Lactic Acid-Producing Organisms and Preparations.

*Dosage.*—Three or more vials daily. When used externally the culture should be liberally applied directly to the diseased

area and in ordinary nose and throat affections the contents of one vial may be employed at each treatment. The culture is marketed in packages of six and in packages of twenty vials. The culture must be kept in a cold place and should be used prior to the date stamped on the package.

Manufactured by Lederle Antitoxin Laboratories, New York (Schieffelin & Co., New York). No U. S. patent or trademark.

The culture is grown on one of the following mediums: calcium carbonate lactose broth, calcium carbonate dextrose broth, calcium carbonate Cohendy broth, or Cohendy broth.

The material for one of the above-mentioned broths is sterilized for thirty minutes on three successive days and then placed in the incubator for at least forty-eight hours to determine its sterility before using. The material is then put into large flasks, inoculated from test tube cultures of the bacillus and incubated at 37 C. for from twenty-four to ninety-six hours. It is then tested to see that it is free from contaminating organisms.

The preparation is of a light yellow color and has the odor and taste of the particular medium employed as its base.

The material should be inoculated into milk and into the above-mentioned mediums in test tubes and smeared on Cohendy agar. The cultures should be examined microscopically for the detection of contaminating organisms.

**CULTURE OF BULGARIAN BACILLUS**—Mulford.—A pure culture in tubes of *Bacillus bulgaricus*.

*Actions and Uses.*—The culture of Bulgarian bacillus-Mulford is designed for internal administration and for direct application to body cavities, abscesses and wounds. See preceding general article, Lactic Acid-Producing Organisms and Preparations.

*Dosage.*—One tube of the culture in 3 tablespoonfuls of water containing a lump of sugar or taken in a half or full glass of milk. This dose should be repeated morning and evening after meals. The tubes must be kept in a cold place and should not be used after the date stamped on the package.

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

**GALACTENZYME TABLETS.**—Tablets *Bacillus Bulgaricus*—Abbott.—Tablets containing a practically pure culture of *Bacillus bulgaricus* (Type A).

*Actions and Uses.*—Galactenzyme tablets are designed for internal administration in the treatment of intestinal fermentative diseases by the Bulgarian bacilli, with the design of obtaining the growth in sufficient number of the bacilli in the alimentary tract, so as to secure their characteristic action against putrefactive fermentation by the production of lactic acid.

*Dosage.*—One, two or three tablets three times a day with meals. The diet should be regulated to meet the condition which may be present.

Galactenzyme tablets are marketed in bottles, each containing 100 tablets. The tablets must be kept in a cold place and are not guaranteed beyond the date stamped on the label.

Manufactured by the Abbott Laboratories, Chicago. No U. S. patent or trademark.

Cultures of a pure and virile strain of *Bacillus bulgaricus* (Type A) are grown on sterilized milk. This milk culture of the organism is mixed with purified milk sugar. The mixture is dried in a stream of sterile, filtered air, at low temperature, and the dried product compressed into tablets under aseptic conditions.

**GALACTENZYME BOUILLON.**—Suspension of *Bacillus Bulgaricus*-Abbott.—A pure culture in vials of *Bacillus bulgaricus* (Type A), each vial containing about 6 Cc.

*Actions and Uses.*—Galactenzyme bouillon is designed for internal administration in the treatment of intestinal fermentative diseases with the design of obtaining the growth in sufficient number of the bacilli in the alimentary tract so as to secure their characteristic action against putrefactive fermentation. It is also used for topical applications in nasal, aural, throat, urethral and other affections when the use of such a culture is indicated.

*Dosage.*—The contents of one vial in a little sweetened water or milk, once or twice daily, preferably on an empty stomach. A small quantity of carbohydrate food should be included in the dietary.

Galactenzyme bouillon is supplied in packages of twelve vials. It must be kept in a cold place, and is not guaranteed beyond the date stamped on the label.

Manufactured by the Abbott Laboratories, Chicago. No U. S. patent or trademark.

Cultures of a pure and virile strain of *Bacillus bulgaricus* (Type A) are grown in a specially prepared bouillon.

**KEFIR FUNGI.**—A mixture of bacteria and yeasts capable of causing lactic acid fermentation of milk.

*Actions and Uses.*—See preceding general article, Lactic Acid-Producing Organisms and Preparations.

*Dosage.*—Kefir kumyss may be prepared by adding active kefir grains to fresh cows' milk, kept at a temperature of 21 to 27 C. until the effect of fermentation becomes apparent by the rising of the grains to the surface. The grains may then be strained off, and the milk, which now contains sufficient yeast-cells to insure continuance of the fermentation, left to itself in well-corked bottles.

Kefir occurs in the form of white irregular roundish bodies of the size of a walnut, with a very rough, furrowed surface, and of a tough

gelatinous consistency. The substance contains *Saccharomyces cerevisiae* (Heyden), *Bacillus acidi lactici* (Hueppe), *Dispora Caucasica* (Kern). It acts on milk as follows: Fat, salt and water of the milk remain unaffected. The lactose is gradually decreased and the lactic acid increased. Alcohol is produced along with carbon dioxide; 10 per cent. of the casein is converted into acid albumin and peptones, 10 per cent. into hemialbumose and the rest loses its lime.

**LACTAMPOULE.**—A pure culture in ampules, of the *Bacillus bulgaricus*, each ampule containing about 12 Cc.

*Actions and Uses.*—Lactampoules are designed for the inoculation of milk or other culture medium, or for direct application to body cavities. See preceding general article, Lactic Acid-Producing Organisms and Preparations.

*Dosage.*—The ampules must be kept in a cold place, and are not guaranteed beyond the date stamped on the package.

Manufactured by Fairchild Bros. & Foster, New York. No U. S. patent or trademark.

The bacilli are obtained by the usual bacteriologic method, the growth of the bacilli on modified Cohendy peptone-sugar-broth medium.

**LACTIC BACILLARY TABLETS-FAIRCHILD.**—Tablets said to be made from a practically pure culture of *Bacillus bulgaricus*.

*Actions and Uses.*—See preceding general article, Lactic Acid-Producing Organisms and Preparations.

*Dosage.*—One or two tablets before or after meals. The tablets should be kept in a cold place and should not be used after the date given on the label.

Manufactured by Fairchild Bros. & Foster, New York. No. U. S. patent or trademark.

The culture of the Bulgarian bacillus is obtained by inoculation and incubation on modified Cohendy peptone-sugar-broth medium. This culture is reduced to a pulverulent form by the addition of sterile lactose, desiccated and compressed. The tablet is friable and contains an abundance of the true Bulgarian lactic acid bacterium.

In the standardization of this product 1 tablet is placed, under aseptic precautions, in 100 Cc. of carefully sterilized centrifuged milk in the sterile flask and kept in the thermostat for forty-eight hours at 40 C.

After incubation for about twenty-four hours the milk should form a coagulum with some slight separation of serum; after about forty-eight hours the milk develops the acidity, about 2 per cent. actual lactic acid, characteristic of the Bulgarian sour milk; and under the microscope shows abundance of the Bulgarian bacilli. This fermented milk by vigorous agitation forms a homogeneous thick fluid, of a marked sour taste, free from bitterness, or sliminess, or objectionable physical characteristics.

**SWAN'S BACILLUS BULGARICUS.**—A pure culture in tubes of *Bacillus bulgaricus*, each tube containing about 4 Cc.



*Actions and Uses.*—Swan's *Bacillus bulgaricus* is designed for internal administration and for direct application to body cavities, abscesses and wounds. See preceding general article, Lactic Acid-Producing Organisms and Preparations.

*Dosage.*—Internally, the contents of one tube three or four times a day. The culture is supplied in boxes of twelve tubes. The tubes must be kept in a cool place and are not guaranteed beyond the date stamped on the package.

Manufactured by Swan-Myers Company, Indianapolis, Ind. No U. S. patent or trademark.

A vigorous strain of the Type A *Bacillus bulgaricus* is grown on a medium representing a clear neutral whey with the addition of 2 per cent. Merck's glucose and 1 per cent. peptone.

**VITALAIT STARTER.**—A culture in vials of *Bacillus bulgaricus* and *Streptococcus acidi-lactici* in symbiosis.

*Actions and Uses.*—Vitalait starter is intended for the home preparation of fermented milk.

*Dosage.*—The vitalait starter (sufficient to prepare from 1 to 3 quarts of fermented milk) is sent on request of the physician to the patient twice a week, with directions for the preparation of the fermented milk. Vitalait starter is sent within three hours of the time incubation is complete, and must be used within five days from the date of mailing stamped on the label.

Manufactured by The Vitalait Laboratory, Inc., Newton Centre, Mass. No U. S. patent or trademark.

*Bacillus bulgaricus* and *Streptococcus acidi-lactiti* are grown in skim milk without the addition of any chemical, and the culture sent out represents these organisms growing in this medium.

**LANOLIN.**—A nonproprietary name applied to Hydrous Wool Fat, U. S. P. For description see the U. S. Pharmacopeia under Adeps Lanae Hydrosus.

**LIQUID PETROLATUM.**—*Petrolatum Liquidum.*—Liquid petrolatum is described in the U. S. Pharmacopeia. For description see the U. S. Pharmacopeia or Useful Drugs.

*Actions, Uses and Dosage.*—See Useful Drugs.

**Liquid Petrolatum-Merck.**—A nonproprietary brand of liquid petrolatum made from American petroleum.

Merck & Co., New York.

It is colorless, non-fluorescent, practically odorless and tasteless. Specific gravity 0.855 at 15 C. or 0.846 at 25 C. It complies with the tests of the U. S. Pharmacopeia.

Liquid Petrolatum-Squibb, Heavy (Californian).—A non-proprietary brand complying with the standards for liquid petrolatum, U. S. P., made from Californian petroleum and claimed to be composed essentially of hydrocarbons of the naphthene series. For description see the U. S. Pharmacopeia or Useful Drugs.

E. R. Squibb & Sons, New York.

Liquid petrolatum-Squibb, heavy (Californian) is colorless, non-fluorescent, practically odorless and tasteless. Specific gravity 0.886 to 0.892 at 15 C., or 0.881 to 0.887 at 25 C. It complies with the tests of the U. S. Pharmacopeia and in addition to the following test:

If 5 Cc. of sulphuric acid, U. S. P., are mixed with 5 Cc. of nitric acid, U. S. P., in a 25 Cc. glass-stoppered cylinder, and after the mixture has cooled, 5 Cc. of liquid petrolatum-Squibb be added and the mixture shaken for thirty seconds, neither the test reagent nor the liquid petrolatum should assume a color deeper than canary yellow, nor should any matter separate at the junction of the liquids.

## LITHIUM SALTS

The lithium ion acts as a depressant on the heart, but less so than the potassium ion. It acts as a gastric and intestinal irritant, and disturbances of the alimentary tract have been produced by the administration of lithium salts. While lithium bromide, lithium iodide and lithium citrate have had some vogue in medicine, these salts possess no advantage over the corresponding potassium or sodium salts and have been practically abandoned. Owing to the citrate radical, lithium citrate, like the citrates of sodium, potassium, calcium, etc., has some diuretic action which depends on its conversion to carbonate in the body with its consequent tendency to decrease the acidity of the urine. The use of lithium salts as uric acid solvents was based on a misconception of chemical facts. There is no reliable clinical evidence that lithium salts increase the excretion of uric acid by the kidney except possibly through a diuretic action; and this is not superior to that of corresponding potassium or sodium salts. Experimental work has failed to show that lithium salts cause the absorption of deposited urates in gouty topi.

**BISMUTH AND LITHIUM CITRATE (Soluble) Wellcome Brand.**—See Bismuth Compounds.

## MANGANESE COMPOUNDS

Depending on their oxidizing power, permanganates—potassium permanganate, U.S.P. and zinc permanganate, N.N.R.—are used as germicides and disinfectants and also for their styptic action. Compounds of manganese, particularly manganese dioxide (precipitated manganese dioxide, U.S.P.), have been used for systemic effects, especially as emmenagogues and hematinics; but the evidence for their usefulness is not very convincing.

The use of manganese dioxide as an emmenagogue is highly recommended by some authors on the supposition that it increases the flow of blood to the pelvic organs. Since manganese is but very little absorbed, and in the form of the insoluble oxide can have very little local action, it is difficult to conceive how it could produce this effect. It has been claimed that manganese is a normal constituent of human blood, but the researches of Bertrand and Medigreceanu have shown the amount to be extremely small, not exceeding 0.05 mg. per liter (*Ann. de l'Inst. Pasteur*, 26: 1013, 1912).

The various compounds of manganese have been used, either as substitutes for, or in combination with iron, in the treatment of anemia, chlorosis, etc. The evidence of this action is not strong; but it is possible, since traces of manganese are absorbed (Casamajor: J. A. M. A., March 1, 1913, p. 646), that these promote the formation of hemoglobin. The phenomena in acute poisoning by soluble salts of manganese are entirely local, that is, exerted on intestines and kidneys.

While manganese has generally been administered internally in the form of potassium permanganate or of manganese dioxide, its administration in the form of manganous compounds—manganous sulphates, U.S.P.—or in complex combination, similar to the complex iron combinations (which see) is more rational.

**FERRO-MANGAN.**—See Iron Salts, Complex.

## MEDICINAL FOODS

Medicinal foods are preparations of alimentary substances designed to supply special needs in the nutrition of the sick. The estimations of the nutritional values of these medicinal foods are here based on the calorific values of their carbohydrate, fat and protein contents, and do not include the calorific values of any alcohol or glycerin they may contain. In these computations the following factors are used as the equivalents in large calories of 1 Gm. of foodstuff: for carbohydrate, 4.1; for fat, 9.2; for proteins, 4.1. The protein content of these foods has generally been estimated by multiplying the nitrogen content by 6.25. It is not, however, conceded that all of the nitrogen represents nutritional nitrogenous matter. They may be divided into the following classes: liquid mixed foods, dry protein foods, carbohydrate foods and diabetic foods.

### Liquid Mixed Foods

These preparations contain varying, often rather small amounts of proteins and carbohydrates, preserved by alcohol. With predigested foods it is important that the protein substances should be rendered soluble by means of enzymes or

by some process which will ensure the formation of nutritious and nontoxic products. The hydrolysis of proteins may also be effected by means of acids or superheated steam; but these products should be used as medicinal foods only when their composition and behavior are known, since dangerous toxic symptoms have been reported from the use of mixtures obtained in this way.

*Actions and Uses.*—The nutritive value of these medicinal foods should be considered as based on their carbohydrate and protein content, exclusive of alcohol or glycerin. The Council has decided that no liquid medicinal or predigested food shall be given consideration which contains less nutritive value, exclusive of alcohol and glycerin, than milk; and at least one-fourth of this should reside in nitrogenous constituents. For practical purposes glycerin can scarcely be considered as a practical food, although there are a number of experiments on record to indicate that it influences metabolism and can be utilized by the organism to a limited extent. While the value of alcohol in the treatment of disease is fully appreciated, its value in disease as a food product pure and simple is an open question. It probably acts as a saver of fat and carbohydrate, but it cannot act as a tissue builder.

The importance of predigestion has been exaggerated. It has been assumed that in fevers the digestive powers are much reduced. It is now known, however, that the digestion and utilization of food in typhoid fever, for instance, are far less disturbed than has been the general belief and appear to be, often at least, nearly normal. In some cases, however, the stomach may tolerate such predigested foods better than others; they may at times be added to other nutriment with advantage, at least for variety.

*Dosage.*—None of the commercial liquid medicinal or predigested foods contains sufficient food material to maintain normal nutrition. A man doing moderate work requires an amount of food which furnishes energy equal to 3,000 calories per day, and while this amount may not be required in sickness, it is reasonable to assume that it should not fall much below 1,500 calories per twenty-four hours for any length of time. The available dose of the preserved liquid foods is limited by the alcoholic content. This is often so high that the dosage needed to supply the energy requirements would also keep the patient in a continuous alcoholic stupor. No more should be given than can be appropriated by the patient without showing signs of alcoholic intoxication. It should be remembered, therefore, that the patient is receiving a starvation diet when these preparations are given in ordinary doses as the only food. Indeed, unless the daily dose advised contains at least 100 calories, exclusive of alcohol and glycerin, a preparation should not be depended on as of noteworthy importance in helping to sustain life



even for a very limited period. (Medicinal Foods, Reports of the Council on Pharmacy and Chemistry, 1905-1908, p. 63; J. A. M. A., May 11, 1907, p. 1612).

**ENEMOSE.**—A sterile liquid containing approximately: the nitrogenous substances from beef and wheat, 12 per cent.; carbohydrates from wheat, 46 per cent.; ash (phosphates, etc.) 4.5 per cent.; in a noncoagulable, diffusible and assimilable form. Enemose is stated to contain the ingredients of physiologic sodium chloride solution, in amounts such that when diluted for use it has the composition of physiologic sodium chloride solution; also 1 part salicylic acid in 1,000 parts, or about  $\frac{1}{2}$  grain per fluidounce.

*Actions and Uses.*—Enemose is a nutrient especially designed for colonic alimentation. The nutritive value of 500 Gm. of enemose corresponds approximately to 1,190 calories, of which 250 are due to proteins and 940 to carbohydrates. The same quantity of milk represents 360 calories, of which 72 are due to protein and 98.4 to carbohydrates.

*Dosage.*—Enemose is made ready for injection by simply dissolving in warm water at the moment required for use—1 volume (1 ounce vial) of enemose to 4 volumes (ounces) of water gives a solution of nutrients whose potential energy is equivalent to about 73 calories, of which 15 are furnished by the protein matter and 56 by the carbohydrates.

Enemose may be dissolved in hot water and allowed to cool to the proper temperature for injection.

Enemose is put up in vials, each containing 1 ounce, which should not be opened until required.

Manufactured by Fairchild Bros. & Foster, New York. No U. S. patent. U. S. trademark applied for.

Enemose is stated to be free from fat, sucrose and alcohol.

In the preparation of enemose, lean beef and whole wheat are said to be subjected to the action of the gastric, pancreatic and intestinal mucosa extracts, the solution sterilized, clarified and concentrated. The carbohydrates thus obtained are said to consist of maltose and dextrans; the proteins present the entire group of derivatives of enzymic digestion beyond albumose.

**LIQUID PEPTONIDS.**—A medicinal food prepared from beef, milk and wheat, containing from 5.25 per cent. nitrogenous matter (nitrogen  $\times$  6.25), 13.8 per cent. carbohydrates (glucose, lactose and sucrose) and 17.9 per cent. alcohol by volume (14.5 by weight).

*Actions and Uses.*—See general article, Medicinal Foods (Liquid Mixed Foods). The nutritive value, derived from the protein digestion products and carbohydrates, maltose, lactose and dextrin, exclusive of alcohol, of 500 Gm. of liquid peptonoids corresponds approximately to 410 calories, of which 107 are due to protein and 285 to carbohydrates. The

same quantity of milk represents 360 calories, of which 72 are due to protein and 98.4 to carbohydrates and the rest to fats.

*Dosage.*—From 15 to 30 Cc. (4 to 8 fluidrachms) from three to six times a day. Children in proportion.

Manufactured by the Arlington Chemical Co., Yonkers, N. Y. U. S. trademark.

This food is said to be made from beef, milk and wheat by digesting the protein with pepsin and pancreatin and the carbohydrates with pancreatin and malt diastase.

It is a light brown fluid of aromatic taste and odor and acid in reaction. Its specific gravity is 1.047 to 1.049.

**PANOPEPTON.**—A medicinal food prepared from beef and wheat, containing 6.5 per cent. of nitrogenous matter (nitrogen  $\times$  6.25), 16.5 per cent. of carbohydrates and 19.7 per cent. alcohol by volume (15 to 16 per cent. by weight).

*Actions and Uses.*—See general article, Medicinal Foods (Liquid Mixed Foods). The nutritive value derived from the protein digestion products, of 500 Gm. of Panopepton corresponds approximately to 472 calories, of which 132 are due to protein and 340 to carbohydrates. The same quantity of milk represents 360 calories, of which 72 are due to protein, 98.4 to carbohydrates and the rest to fats.

*Dosage.*—From 4 to 8 Cc. (1 to 2 fluidrachms) several times a day and at bedtime; for infants from a few drops to 2 Cc. (30 minims).

Manufactured by Fairchild Bros. & Foster, New York. U. S. trademark.

Panopepton is said to be prepared from beef and wheat by digestion with gastric and pancreatic juices. The substance obtained by the digestion is mixed in fixed proportion of protein and carbohydrate, sterilized, concentrated *in vacuo* and dissolved in sherry wine.

It is a deep brown fluid, acid in reaction and possessing an odor and taste of sherry wine. Its specific gravity is 1.063 to 1.023.

## Dry Protein Foods

*Actions and Uses.*—The predigestion of protein may be of value in conditions in which the digestive power of the stomach is lacking. In such cases meat fiber fails of digestion and may be irritating to the intestine. Predigested protein is also of value for use in rectal alimentation. Dry proteins, predigested or not, may be used to increase the protein content of soups, gruels and other liquid foods.

*Dosage.*—The dosage of dry proteins is determined by the tolerance of the patient and by his nutritional needs. Each gram of dry protein produces about 4.1 calories. Care should be taken that the protein is not destroyed by putrefactive processes in the intestines, which may not only lessen the nutritive value of the food, but also act on the organism in a deleterious manner by the toxins formed.

The dry proteins are presented in the following principal forms: meat, predigested and in the form of a dry powder; casein, usually rendered more soluble by partial conversion to sodium caseinate; legumes, such as flour made from the soja bean; mixtures containing dry proteins mixed with carbohydrates or other nutrients.

**CIOSE.**—A dry, completely soluble protein product of beef, separated from extractives and containing 83 to 85 per cent. actual protein.

*Actions and Uses.*—The nutritive value of 500 Gm. of ciose, calculated on the protein content, corresponds approximately to 1,722 calories. The same quantity of milk represents 360 calories, of which 72 are due to protein and 98.4 to carbohydrates. Ciose is especially designed as a means of augmenting the protein of any desired diet. It may be added to soups and broths of beef, chicken, cereals, vegetables, etc., at the moment of taking; it may also be added to any prepared food, the protein of which it is desired to raise; or given in wine. It may be taken in hot water with the addition of salt, pepper, celery or any other condiment.

Manufactured by Fairchild Bros. & Foster, New York. No U. S. patent. U. S. trademark No. 47,774.

In the preparation of ciose the minced washed fiber of fresh raw beef is subjected to digestion under the action of an extract of the fresh gastric gland and under conditions of time, temperature and reactions approximating those of bodily digestion; the solution thereby obtained is sterilized by boiling and then filtered and by this means the solution is freed from enzymes and from coagulable substances, and reduced to dryness *in vacuo*.

Ciose occurs in light, yellowish-white scales. It is easily soluble in water, forming a solution having a faintly acid reaction.

**DRY PEPTONIDS.**—A medicinal food prepared from beef, milk and wheat, containing 40 per cent. of proteins and 53 per cent. of carbohydrates.

*Actions and Uses.*—See general article, Dry Protein Foods. The nutritive value of 500 Gm. of dry peptonoids corresponds approximately to 1,905 calories, of which 820 are due to protein and 1,085 to carbohydrates and fat. The largest dose usually given (16 Gm.), therefore, is equivalent to about 61 calories. It is claimed to be especially useful for nutrient enemas.

*Dosage.*—For an adult from 8 to 16 Gm. ( $\frac{1}{4}$  to  $\frac{1}{2}$  ounce), taken in water, milk, wine, broths, soups, etc., also in gruels, in which case it should first be dissolved in a small quantity of water.

Manufactured by the Arlington Chemical Co., Yonkers, N. Y. U. S. trademark Oct. 17, 1882.

Dry peptonoids is said to be made from beef, milk and wheat, by digesting the protein with pepsin and pancreatin and the car-

bohydrates with pancreatin and malt diastase. The resultant solutions are assayed, mixed in proper proportions and, the acid used in the digestion having been neutralized, concentrated *in vacuo*, sterilized, dried and brought to uniform composition by the addition of milk sugar.

It consists of light brown granules of pleasant odor and taste and is very soluble in water.

**LAROSAN-ROCHE.**—Stoeltzner's Casein Calcium.—Calcium caseinate containing calcium equivalent to 2.5 per cent. calcium oxide.

*Actions and Uses.*—The diarrheal diseases of infancy are now generally treated by dietetic measures. A useful food is that made from the curd of milk and diluted buttermilk, the resultant mixture containing a moderate amount of fat, a small amount of sugar and a large amount of protein (casein) and salts, particularly salts of calcium. Such a mixture being difficult to prepare in a private home, larosan-Roche is offered as a substitute.

*Dosage.*—For infants and children it is administered as Larosan Milk, which is prepared, in accordance with simple directions, with milk and water or gruel in the proportions of one small package ( $\frac{2}{3}$  ounce) larosan-Roche to 1 pint of cow's milk and 1 pint of boiled water or gruel. For adults it is given mixed with milk in the proportions of two small packages ( $1\frac{1}{3}$  ounce) larosan-Roche to 1 quart of milk.

Manufactured by F. Hoffmann-LaRoche and Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York). U. S. patent No. 1,087,515 (February, 1914; expires 1921).

Laroson-Roche is prepared by treating a suspension of casein in water with calcium hydroxide in such quantities as to yield a solution neutral to phenolphthalein and then evaporating to dryness in a special apparatus.

It is a light, white, practically odorless and tasteless powder, soluble in water, yielding a slightly opalescent solution, and neutral to phenolphthalein.

If incinerated, it emits an odor characteristic of burning protein and leaves a residue of calcium oxide which should weigh 2.5 per cent. of the amount of material taken.

It is incompatible with acids.

## Carbohydrate Foods

Prepared carbohydrate foods are used mostly in infant-feeding. They are made by the action of amylolytic enzymes on starch or by other modes of conversion by which the starch is changed into dextrin, maltose or dextrose. The calorific value of these foods is determined on the assumption that 1 Gm. of the dry carbohydrate is equivalent to 4.1 calories.



**BORCHERDT'S MALT SUGAR.**—A mixture containing approximately maltose 87.40 per cent., dextrin 4.35 per cent., protein 4.40 per cent., ash 1.90 per cent., moisture 1.95 per cent.

*Actions and Uses.*—Borcherdt's malt sugar may be used where maltose is indicated in the feeding of infants, particularly in the treatment of constipation. The nutritive value of 500 Gm. of Borcherdt's malt sugar corresponds to approximately 1,985 calories.

*Dosage.*—It may be used in all milk mixtures in the same proportions as lactose (sugar of milk), that is, one ounce of Borcherdt's malt sugar (two tablespoonfuls) to a 20 ounce mixture.

Manufactured by the Borcherdt Malt Extract Co., Chicago. No U. S. patent. U. S. trademark No. 64,467.

Borcherdt's malt sugar is prepared by the action of malt diastase on starch.

It is a pale brownish-yellow powder having a malt odor and a sweet taste. It is somewhat hygroscopic and very soluble in water.

If a few drops of iodine test solution be added to an aqueous solution of Borcherdt's malt sugar (1:10) no reddish-violet or blue color is produced.

The maltose content of Borcherdt's malt sugar is determined according to the method described in U. S. Dept. of Agriculture, Bureau of Chemistry, Bulletin 107, p. 46.

The protein content of Borcherdt's malt sugar is calculated from the nitrogen content ( $N \times 6.25$ ) as determined by the method described in U. S. Dept. of Agriculture, Bureau of Chemistry, Bulletin 107, p. 5.

**DEXTRI-MALTOSE NO. 1, MEAD'S.**—A mixture containing approximately: maltose 52.0 per cent., dextrin 41.7 per cent., sodium chloride 2.0 per cent. and moisture 4.3 per cent.

*Actions and Uses.*—On the claim that maltose is more readily assimilated than other forms of sugar, Mead's dextri-maltose No. 1, is proposed to supplement the carbohydrate of cows' milk. The nutritive value of 500 Gm. of dextri-maltose corresponds to approximately 1,920 calories. The same quantity of milk represents 360 calories.

*Dosage.*—It may be used in all milk mixtures in the same proportions—by weight—as sugar of milk—i. e., 1 ounce of Mead's dextri-maltose No. 1 (2 tablespoonfuls) to a 20-ounce mixture.

Manufactured by Mead Johnson & Co., Evansville, Ind. No U. S. patent or trademark.

**DEXTRI-MALTOSE NO. 2, MEAD'S.**—A mixture containing approximately maltose, 53.1 per cent.; dextrin, 42.6 per cent., and moisture, 4.3 per cent.

*Actions and Uses.*—On the claim that maltose is more readily assimilable than other forms of sugar, Mead's dextri-

maltose No. 2 is proposed for use in the diet of adult invalids. The nutritive value of 500 gm. of Mead's dextrimaltose No. 2 corresponds to approximately 1,960 calories. The same quantity of milk represents 360 calories.

*Dosage.*—Mead's dextri-maltose No. 2 may be used in amounts to meet the carbohydrate requirements of the invalid in place of other carbohydrates.

Manufactured by Mead Johnson & Co., Evansville, Ind. No U. S. patent or trademark.

**DEXTRI-MALTOSE NO. 3, MEAD'S.**—A mixture containing, approximately, maltose, 52 per cent.; dextrin, 41.7 per cent.; potassium carbonate, anhydrous, 2 per cent., and moisture, 4.3 per cent.

*Actions and Uses.*—On the claim that maltose is more readily assimilable than other forms of sugar, Mead's dextrimaltose No. 3 is proposed to supplement the carbohydrate of cow's milk. In the belief that an addition of potassium salts counteracts a tendency to constipation, it is said to be particularly adapted in the feeding of constipated infants. The nutritive value of 500 gm. of Mead's dextrimaltose No. 3 corresponds to approximately 1,920 calories. The same quantity of milk represents 360 calories.

*Dosage.*—Mead's dextri-maltose No. 3 may be used in amounts to meet the carbohydrate requirements of infants in place of other carbohydrates.

Manufactured by Mead Johnson & Co., Evansville, Ind. No U. S. patent or trademark.

Mead's dextri-maltose is prepared by the action of diastase on starch.

It is a pale yellowish-white, granular, odorless powder, having a faintly sweetish taste. It is somewhat deliquescent on exposure to the air. It is soluble in water.

If a few drops of iodine test solution be added to an aqueous solution of Mead's dextri-maltose (1:10) a reddish violet but not a blue color should be produced.

The maltose in Mead's dextri-maltose is determined by the Fehling volumetric method as described in Leach's "Food Inspection and Analysis," Ed. 2, p. 591, but instead of the factor there given the Fehling's solution is standardized against a 0.5 per cent. solution of maltose.

**DEXTROSE.** — *Saccharum Amylaceum.* — d-Glucose. —  $C_6H_{12}O_6 + H_2O$ .—A carbohydrate prepared by the action of dilute acids on starch; it also occurs naturally.

*Actions and Uses.*—Dextrose is quite readily absorbed and may be used in place of cane sugar as a food.

*Dosage.*—180 Gm. (6 oz.) daily.

Dextrose containing a molecule of water of crystallization occurs in white crystalline masses. It is soluble in its own weight of water at 15 C, in 50 parts alcohol (85 per cent.) at 17 C. and in 11 parts at the boiling temperature.

An aqueous solution (1:10) of dextrose should yield after the addition of dilute nitric acid not more than a slight turbidity with either barium nitrate or silver nitrate, and after the addition of ammonia should produce no precipitate with ammonium oxalate.

An aqueous solution (1:20) of dextrose should not change when heated with hydrogen sulphite.

### Foods for Diabetes

The essential purpose of dietetic treatment of diabetes is to abolish glycosuria, hyperglycemia and acidosis by the reduction of the carbohydrate intake. Foods containing not more than 10 per cent. of sugar-forming carbohydrates have generally been regarded as permissible; those containing higher amounts must be used with greater caution. It is therefore necessary that the carbohydrate content of foods for diabetics should be accurately stated. There is no foundation for the claims that special forms of starch, such as oat-meal, toasted bread, or certain proprietary preparations, are any better assimilated than other kinds of starch.

The place of carbohydrates other than glucose and starch, e. g. levulose, inulin, lactose (milk), is not quite so thoroughly investigated, but it is safe to conclude that their superior assimilability is apparent rather than real. They may sometimes be useful for special purposes in the hands of specialists, but in general they should be reckoned with as are the ordinary forms of carbohydrates.

Since in diabetes it is the carbohydrate metabolism which is first and most profoundly altered, it is necessary to know the percentage of utilizable carbohydrate in every food that the patient eats. In all except the milder forms of diabetes, it is also essential to know the quantities of protein and fat, as well as the amount of carbohydrate. It is therefore particularly necessary to know the carbohydrate content of every food used in the treatment of diabetes, and only somewhat less important to know their contents of protein and fat.

It has long been known that sugar can be formed from protein and consequently the protein of the diet must be carefully restricted in quantity, but this requirement has been widely ignored by practitioners. Since the diabetic foods which are low in carbohydrate are generally correspondingly high in protein, they cannot be given to the patients in unrestricted amounts.

Another requirement more recently emphasized is the restriction of fat and the total caloric value of the diet. Often diminution of fat is more important than increase of carbohydrate as a means of combating acidosis. Foods for diabetics are generally concentrated foods, formerly prized on account of their high food value, but now sharply restricted on this very account. Diabetics should not be treated by the use of mere lists of permissible and forbidden foods; the

total diet should be exactly prescribed in carbohydrate, protein, fat, and total calories in accordance with the ability of the individual patient to digest these foods. The chief function of a diabetic bread is to provide a palatable, bread-like vehicle for butter, cheese or the like. A high food value is not important or even desirable. The less utilizable carbohydrate such articles contain the more general may be their use. A high protein content limits the use of such articles in severer cases since in such cases the tolerance for protein must be considered as well as that for carbohydrate. Uniformity of composition from month to month, reliable analytical data, a maximum of surface for a minimum of carbohydrate and protein, palatability, low price and availability are points of chief interest in appraising usefulness of such articles. For the purpose of avoiding too high a ration, bulky substances of low nutritive value are useful in the diet. Such are green vegetables and bran; and such use of cellulose or other indigestible material for the purpose of making up a sufficiently bulky and satisfying diet is largely replacing the former employment of concentrated foods for diabetics. Foods classed in this list contain as a rule not more than approximately 10 per cent. of the nutriment in the form of utilizable sugar-forming carbohydrates.

**GLUTEN FOOD A, Barker's.**—A gluten flour prepared from wheat, containing not more than 4 per cent. of carbohydrates and 87 per cent. of protein.

*Actions and Uses.*—Barker's gluten food A is indicated when a diet practically free from carbohydrates is desired, especially in severe forms of diabetes. It can be taken uncooked or made into muffins.

The nutritive value of 500 Gm. of Barker's gluten food A corresponds approximately to 1,845 calories, of which 1,785 are due to proteins, 80 to carbohydrates and 30 to fat.

Manufactured by Herman Barker, Somerville, Mass. No U. S. patent or trademark.

Barker's gluten food A is made from wheat flour by elutriation.

It is a granular powder practically without odor or taste and is insoluble in water.

**GLUTEN FOOD B, Barker's.**—A gluten flour prepared from wheat, containing not more than 7 per cent. of carbohydrates and 85 per cent. of protein.

*Actions and Uses.*—Barker's gluten food B is indicated when a diet relatively free from carbohydrates is desired, uncooked or made into muffins.

The nutritive value of 500 Gm. of Barker's gluten food B corresponds approximately to 1,917 calories, of which 1,742 are due to protein, 145 to carbohydrates and 30 to fat.



Manufactured by Herman Barker, Somerville, Mass. No U. S. patent or trademark.

Barker's gluten food B is made from wheat flour by elutriation.

It is a granular powder practically without odor or taste and is insoluble in water.

**GLUTEN FOOD C, Barker's.**—A gluten flour prepared from wheat, containing not more than 12 per cent. of carbohydrates and 83 per cent. of protein.

*Actions and Uses.*—Barker's gluten food C is indicated when a diet relatively free from carbohydrates is desired. It can be taken uncooked or made into muffins.

The nutritive value of 500 Gm. of Barker's gluten food C corresponds approximately to 1,970 calories, of which 1,700 are due to protein, 240 to carbohydrates and 30 to fat.

Manufactured by Herman Barker, Somerville, Mass. No U. S. patent or trademark.

Barker's gluten food C is made from wheat flour by elutriation.

It is a granular powder practically without odor or taste and is insoluble in water.

**HEPCO FLOUR.**—A flour prepared from the soy bean, having approximately the following composition: protein, 42.9; carbohydrate, 22.4, of which less than one-half readily yields sugar; fat, 20.8; ash, 5.1; fiber, 4.2; water, 4.6.

*Actions and Uses.*—It is claimed that clinical trials have shown that the carbohydrates in hepcos flour are, in the main, not sugar-producing and that therefore hepcos flour is a suitable food material in cases in which carbohydrates are contraindicated, as diabetes, amylaceous dyspepsia, etc. It has also been suggested for use in the diet in obesity. The nutritive value of 500 Gm. of this flour corresponds approximately to 2,048 calories, of which 700 calories are due to protein, 448 calories to carbohydrate, and 900 calories to fat.

Manufactured by the Waukesha Health Products Company, Waukesha, Wis. No U. S. patent. U. S. trademark No. 103,772.

*Hepco Dodgers.*—A biscuit prepared from and having approximately the same composition as hepcos flour.

*Hepco Grits.*—A granulated "breakfast food" made from and having approximately the same composition as hepcos flour.

To prepare hepcos flour, soy beans are cleaned and cooked with a little salt, then dried and ground. The flour is sifted and reground.

Hepco dodgers are made according to the following recipe: 1½ pounds hepcos flour; ½ teaspoonful of salt; mix well and add ¾ cupful of milk and 1 cupful of cold water; 2 eggs which have been thoroughly beaten; beat the whole mixture together into a cooky batter, roll out to ¼ inch thickness, cut with a cooky cutter and bake on well-buttered tins in hot oven. This recipe will make about three dozen dodgers. The dodgers are made up for shipping purposes by having a pure gelatine mixed in with the flour and then rolled out.

Hepco grits are made according to the recipe for hepco dodgers. The material is thoroughly dried out and put through a bread crumber.

#### LISTERS PREPARED CASEIN DIABETIC FLOUR.

—Milk casein to which has been added a leavening mixture consisting of sodium bicarbonate and potassium bitartrate and also some sodium chloride, and saccharine 0.057 Gm. per 100 Gm.

*Actions and Uses.*—This flour is employed in cases in which carbohydrates are contraindicated, such as diabetes, etc.

The nutritive value of 500 Gm. of Listers prepared casein diabetic flour corresponds to approximately 1,900 calories, of which 1,735 calories are due to protein and 165 calories are due to fat.

The same quantity of milk represents 360 calories, of which 72 are due to protein and 177.6 to fat.

*Dosage.*—Listers prepared casein diabetic flour is said to be adapted for the preparation of muffins. Of these three to six may be consumed daily.

Manufactured by Lister Bros., New York. No U. S. patent or trademark.

### Meat Extracts

Extracts of meat, as originally sold, were obtained by boiling lean beef in water, skimming off the separated fat, filtering from the coagulated proteins and concentrating to a paste. The industry developed through a mistaken notion as to the exact nature of the nitrogenous bodies which went into solution, and before the days of clear ideas on protein chemistry.

In principle the process of manufacture is still the same, but the "extract" is now largely a by-product. Much of it is obtained by boiling down the thin liquid resulting from the cooking of meat in the canning processes, the same water being used for a number of batches of meat. In the stock-yards industries the trimmings and waste too small for the canning process are often converted into extract. Frequently, hearts, liver, lungs, brains and, indeed, anything which will yield an extract are boiled up for the purpose, giving a product of very variable composition.

Roughly speaking, these extracts contain about 20 per cent. of water, 20 per cent. of inorganic salts, and 60 per cent. of organic matters. The average results obtained from a considerable number of analyses of American products are represented by these figures:

Water .....	20 per cent.
Inorganic salts .....	22.5 per cent.
Gelatin and albumose.....	16.5 per cent.
Flesh bases .....	26.4 per cent.
N-free extractives .....	14.6 per cent.

As the figures indicate, the food value of the extracts is rather low, and entirely disproportionate to the high prices at which they are sold. The high selling price is excused by the prevalence of the old notion, carefully fostered, that about 30 pounds of beef must be boiled down to obtain 1 pound of extract. The food value is measured by the albumose and gelatin bodies present, and to some extent by the nitrogen-free extractives. The percentage amounts of these are often lower than given above, while the creatin and similar derivatives are higher.

Meat extracts have some value on account of their flavor, in the preparation of soups and bouillons. They are condiments, rather than foods. To use them as foods, in place of meat, as was attempted in the early days of their manufacture, is perhaps even dangerous because of the content of inorganic salts, especially potassium salts. The classification of these products as foods should be discouraged, but their use as appetizers or condiments in the preparation of foods for the sick may still be admitted.

### Meat Juices

Meat juices proper are obtained by warming chopped meat to a temperature short of the coagulating-point of the muscle proteins present (not above 55 C.) and forcing out the juice by means of strong pressure. These juices as usually made, with or without the addition of water, are intended for immediate consumption. It is difficult to prepare them in a stable form for later use, for their sterilization and filtration eliminate most of the protein. Preservation has also been attempted by the addition of considerable quantities of salt, glycerin or alcohol, all of which are objectionable.

Most, if not all, commercial "meat juices" are apparently made by very different methods from the foregoing. In place of being actual protein solutions they are suspensions of blood, finely divided meat powder, peptone-like bodies and other animal derivatives, preserved by aid of glycerin, alcohol and salts. The name "meat juice" is incorrect when applied to such mixtures, whatever their nutritive value may be, and properly speaking, under this designation they are misbranded. It is possible to prepare mixtures of this description which possess considerable food value, but the method of preservation is of the utmost importance. (Meat and Beef Juices, Reports of the Council on Pharmacy and Chemistry, 1909, p. 137; J. A. M. A., Nov. 20, 1909, p. 1754.)

### MENTHOL COMPOUNDS

**CORYFIN.**—Ethylglycolic Acid Ester of Menthol.—Menthyl Ethylglycolate.— $\text{CH}_2(\text{O.C}_2\text{H}_5).\text{COO}(\text{C}_{10}\text{H}_{19})$ .—The ethylglycolic acid ester of menthol.

*Actions and Uses.*—Soon after its application to the skin or mucous membrane a cooling effect is produced, said to be due to the splitting off of menthol, to which the pharmacologic actions of the remedy are to be ascribed.

Coryfin is said to be useful as a substitute for menthol in nervous headaches, coryza and conditions of hoarseness and pharyngeal irritation.

*Dosage.*—In headache it may be lightly rubbed in or painted on the forehead, avoiding contact with the eyes; in coryza it may be applied to the mucous membrane with a brush or as a spray. In throat affections a few drops (3 or 4) may be placed on a lump of sugar and allowed to dissolve in the mouth, or mixed with tepid water and used as a gargle.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent No. 836,914 (Nov. 27, 1906; expires 1923). U. S. trademark No. 43,416.

Coryfin is prepared by the action of ethyloxyacetyl chloride on menthol. Coryfin is a limpid, colorless oil, having a very faint menthol odor. It boils under 20 mm. pressure at about 155 C. and is soluble in alcohol, ether and chloroform; difficultly soluble in water.

When heated with caustic alkalies it is split up into menthol and ethylglycolic acid. When incinerated on platinum foil it leaves no residue. Aqueous solutions must not have an acid reaction and must be free from chlorine and sulphuric acid.

## MERCURY AND MERCURY COMPOUNDS

The early methods of administering mercury were by mouth and by inunction. The oral method continues to be popular, but often causes troublesome gastro-intestinal symptoms. The inunction method obviates the digestive disturbances, but the amount of the drug absorbed cannot be well controlled and it is practically impossible to introduce an amount sufficient for syphilis.

In recent years the attempt to improve mercurial therapy has been mainly along two lines, the perfection of hypodermic usage and the introduction of the organic compounds.

The original practice of injecting mercuric chloride has not gained a wide endorsement because of the pain inflicted and because the necessity of daily injections was difficult to meet. It has been found that the pain is considerably lessened by the use of mercury combined with the amino-acids and their derivatives, such as the succinimide.

The employment of mercurial salts that are less soluble than the bichloride has enabled the physician to give injections at longer intervals and still ensure a daily absorption of the drug. These insoluble preparations, such as the salicylate and the benzoate, are injected into the muscle, but they are accompanied by no little pain.

The organic compounds of mercury, such as mercurool, are said to be less irritating to the gastro-intestinal tract than



the inorganic salts. Further experience will be necessary to determine their real value.

### Mercuric Compounds, Organic

**MERCUROL.**—Hydrargyri Nucleinas.—Mercury Nucleinate.—An organic compound of mercury with nucleinic acid from yeast, containing 20 per cent. of metallic mercury.

*Actions and Uses.*—Mercurool does not coagulate albumin; it has marked bactericidal power and possesses the pharmacologic action of soluble mercury compounds.

It is said to be useful as a local antiseptic application and as an antisyphilitic remedy.

*Dosage.*—From 0.3 to 0.12 Gm. ( $\frac{1}{2}$  to 2 grains).

Manufactured by Parke, Davis & Co., Detroit. U. S. patent No. 637,355 (expired).

*Mercurool Tablets,  $\frac{1}{4}$  gr.*—Each tablet contains mercuriol 0.016 Gm. ( $\frac{1}{4}$  grain).

*Mercurool Tablets,  $\frac{1}{2}$  gr.*—Each tablet contains mercuriol 0.03 Gm. ( $\frac{1}{2}$  grain).

*Mercurool Tablets, 1 gr.*—Each tablet contains mercuriol 0.065 Gm. (1 grain).

*Mercurool Tablets, 2 grs.*—Each tablet contains mercuriol 0.13 Gm. (2 grains).

*Mercurool with Potassium Iodide Tablets.*—Each tablet contains mercuriol  $\frac{1}{4}$  grain and potassium iodide 1 grain.

Mercurool is prepared by adding a solution of mercuric chloride to an alkaline solution of nuclein, containing an excess of alkali, precipitating the resulting nucleinate of mercury by the addition of alcohol and a concentrated solution of a neutral salt (sodium chloride), separating the precipitate, washing and drying it.

It is a brownish-white powder, soluble in water, especially in warm water, insoluble in alcohol. Its watery solution has a distinct metallic taste, a weak alkaline reaction, and is not precipitated by alkalis, nor by albuminous liquids.

The mercury in this preparation resists the action of hydrogen sulphide to a marked degree.

### Mercuric Compounds, Inorganic

**MERCURIALIZED SERUM-MULFORD.**—A solution of mercuric chloride in normal horse serum, diluted with physiologic sodium chloride solution.

*Actions and Uses.*—Mercurialized serum-Mulford is proposed for the treatment of syphilis, particularly the cerebrospinal type. This is an attempt to produce a preparation which, while therapeutically active, is noncorrosive, produces low toxicity and slight local irritative action, does not coagulate serum albumin, and which consequently is adapted to intraspinal use and can be used intravenously without danger of phlebitis.

*Dosage.*—Intraspinaly, 30 Cc. of a solution, the dose containing the equivalent of 0.0013 Gm. ( $\frac{1}{50}$  grain) mercuric chloride, after *first* withdrawing sufficient spinal fluid to reduce the pressure to 30 mm. (water). The dose may be increased, when tolerance is established, to 30 Cc. of a stronger solution, the dose containing the equivalent of 0.0026 Gm. ( $\frac{1}{25}$  grain) mercuric chloride. Intramuscularly or subcutaneously 2 or 4 Cc. of solution, the dose containing the equivalent of 0.0055 Gm. ( $\frac{1}{12}$  grain), or 0.011 Gm. ( $\frac{1}{6}$  grain), mercuric chloride.

Manufactured by the H. K. Mulford Company, Philadelphia, Pa. No U. S. patents or trademarks.

*Mercurialized Serum-Mulford, No. 1.*—For intraspinal use. Each package contains one 30 Cc. double ended vial, containing the equivalent of 0.0013 Gm. ( $\frac{1}{50}$  grain) mercuric chloride, in 30 Cc. of horse serum.

*Mercurialized Serum-Mulford, No. 5-A.*—For intramuscular or subcutaneous use. Each package contains one syringe with the equivalent of 0.0054 Gm. ( $\frac{1}{12}$  grain) mercuric chloride, in 2 Cc. of horse serum.

*Mercurialized Serum-Mulford, No. 5-B.*—For intramuscular or subcutaneous use. Each package contains one syringe with the equivalent of 0.011 Gm. ( $\frac{1}{6}$  grain) mercuric chloride, in 4 Cc. of horse serum.

*Mercurialized Serum-Mulford, No. 6.*—"Hospital Size Package" for intramuscular or subcutaneous use. Each package contains ten syringes, each containing the equivalent of 0.011 Gm. ( $\frac{1}{6}$  grain) mercuric chloride, in 4 Cc. of horse serum.

Mercurialized serum-Mulford is prepared by adding to a solution of mercuric chloride sufficient normal horse serum to dissolve the precipitate first formed and then diluting to the desired volume with physiologic sodium chloride solution.

**MERCURIC BENZOATE.** — Hydrargyri Benzoas. — Hydrargyrum Benzoicum. —  $\text{Hg}(\text{C}_6\text{H}_5\text{COO})_2 + \text{H}_2\text{O}$ . — The mercuric salt of benzoic acid.

*Actions and Uses.*—The same as those of mercuric chloride.

*Dosage.*—Mercuric benzoate has been said to be useful for hypodermic use and in gonorrhea. In urethral cases the solution may be 1:2,000 or 1:1,000 with an equal quantity of sodium chloride. For hypodermic injection a solution having the following composition may be used: mercury benzoate, from 0.02 to 0.03 Gm.; sodium chloride, 0.01 Gm.; cocaine hydrochloride, 0.15 Gm.; distilled water, 40 Cc.

Ten Gm. glacial acetic acid are diluted with 100 Cc. water and 10 Gm. yellow mercuric oxide added and the mixture agitated until solution is effected. Fourteen Gm. sodium benzoate are dissolved in 100 Cc. water and added to the mercury solution. The precipitate which forms is collected and washed with water till free from acid and dried at 100 C.

Mercuric benzoate is a white crystalline powder, slightly soluble in water, yielding a weakly acid solution, but insoluble in alcohol or ether. At 20 C. a 10 per cent. solution of sodium benzoate dissolves 1 per cent. of its weight of mercuric benzoate. Heated with alcohol it is decomposed into a basic salt of a yellow color.

A solution of 1 Gm. mercuric benzoate and 0.5 Gm. sodium chloride in 20 Cc. water yields a black precipitate with hydrogen sulphide and with ferric chloride solution it yields a fawn-colored precipitate of ferric benzoate.

A solution produced by shaking 1 Gm. mercuric benzoate with 20 Cc. water should not produce more than a faint turbidity when added to silver nitrate solution, acidified with nitric acid (limit of chloride). Two Cc. of a similar solution when mixed with ferrous sulphate solution and then concentrated sulphuric acid added so as to form a layer beneath, should produce no brown coloration as the zone of contact of the two solutions (*nitrates*).

**Mercury Benzoate-Merck.**—A brand of mercuric benzoate. Merck & Co., New York, distributors. No U. S. patent or trademark.

**MERCURIC CYANIDE.** — *Hydrargyri Cyanidum.* — *Hydrargyrum Cyanatum.*— $\text{Hg}(\text{CN})_2$ .—The mercuric salt of hydrocyanic acid.

*Actions and Uses.*—Mercuric cyanide has been reported to be as actively antiseptic as mercuric chloride and to be less irritating; but this has been questioned. It is used locally and internally like mercuric chloride.

*Dosage.*—Internally from 0.004 to 0.008 Gm. ( $\frac{1}{16}$  to  $\frac{1}{8}$  grain); locally, solutions of from 1:4,000 to 1:2,000 may be used for applications to the eye or mucous membranes; from 25 to 35 minims of a 1 per cent. solution may be used hypodermically without causing local irritation. Death has occurred from the use of a vaginal injection containing 0.9 Gm. (14 grains) of mercuric cyanide.

In diphtheria and croup it is used in 0.01 per cent. solution as a gargle or internally in doses of 0.0005 Gm. to 0.001 Gm. (0.0077 to 0.0154 grain). In fibrinous rhinitis it is used on a tampon in 0.04 per cent. solution.

Prussian blue and mercuric oxide in water are boiled until the mixture is brown; the mixture is filtered, acidified with hydrocyanic acid, evaporated and allowed to crystallize in a cool place. It is also prepared by the action of hydrocyanic acid on mercuric chloride. It occurs in colorless or white, prismatic crystals, odorless and having a bitter, metallic taste (the salt is exceedingly poisonous). It is darkened on exposure to light; is soluble at 15 C. in 12.8 parts of water and in 15 parts of alcohol, in 3 parts of boiling water and in 6 parts of boiling alcohol; very sparingly soluble in ether.

When slowly heated in a glass tube the salt decrepitates and decomposes into metallic mercury and inflammable cyanogen gas, which burns with a purple flame. On further heating the blackish residue, consisting of para-cyanogen with globules of metallic mercury, is wholly dissipated. If 1 part of the salt be gently heated with 1 part of iodine in a dry test-tube it will produce at first a yellow sublimate, which afterward becomes red, and above this a sublimate of colorless, needle-shaped crystals. On adding hydrochloric acid to the aqueous solution of the salt the odor of hydrocyanic acid is evolved. A 5 per cent. aqueous solution of the salt should be neutral to litmus paper and should not yield, on the gradual addition of a few drops of potassium iodide test solution, either a red or a reddish precipitate, soluble in an excess of the precipitant, nor should it yield a white

precipitate with silver nitrate test solution (*mercuric chloride*). If mercuric cyanide be dissolved in an aqueous solution of sodium chloride the addition of phenolphthalein to this solution should produce no red coloration (*mercuric oxide*). Ammonia should not color an aqueous solution blue (*copper*) nor should a solution of copper give a brown color or precipitate (*potassium ferrocyanide*). The presence of large quantities of potassium sulphate may be demonstrated by igniting, leaching the ash and testing the filtrate with barium. Dilute sulphuric acid should not liberate hydrocyanic acid (*potassium cyanide*). Ammonia should dissolve mercuric cyanide without producing a white precipitate (*oxycyanide*).

**Mercury Cyanide-Merck.**—A nonproprietary brand complying with the standards for mercuric cyanide.

Merck & Co., New York, distributors.

**MERCURIC OXYCYANIDE.**—*Hydrargyri Oxycyanidum*.—*Hydrargyrum Oxycyanatum*.— $\text{Hg}(\text{CN})_2\text{HgO}$ .—A basic-mercuric salt of hydrocyanic acid.

**Actions and Uses.**—Mercuric oxycyanide is recommended as a substitute for mercuric chloride. Its antiseptic power is said to be greater and it is claimed to be less irritating than mercuric chloride, because it does not act on albumin to the same extent. It has the advantage over the chloride that it does not corrode steel instruments.

**Dosage.**—It may be given by hypodermic injections in the same doses as mercuric chloride or may be applied locally in solution, 1 : 5,000 or slightly stronger.

Mercuric oxycyanide occurs as a white, or nearly white, microcrystalline powder, soluble in about 80 parts of water, yielding a solution alkaline to litmus. Boiled with a mixture of sodium hydroxide, ferrous sulphate and ferric chloride solutions, cooled and then treated with hydrochloric acid, mercuric oxycyanide yields a blue precipitate. A saturated solution yields a white precipitate with ammonium chloride soluble in an excess of the precipitant. Tannic acid solution produces at first a deep yellow color, then gradually a tan colored precipitate. Hydrogen sulphide and ammonium sulphide both produce a black precipitate in an aqueous solution of mercuric oxycyanide. Potassium iodide solution when added to a sodium of mercuric oxycyanide yields a red precipitate soluble in excess of the iodide. An aqueous solution should not respond to tests for chloride, nor should 0.2 Gm. leave a weighable residue when ignited.

If 0.5 to 1 Gm. of mercuric oxycyanide be digested with 1 Gm. sodium chloride in 20 Cc. water the titration of this solution, with tenth-normal hydrochloric acid, methyl orange or paranitrophenol being used as indicator, should indicate the presence of not less than 96 per cent. mercuric oxycyanide. Each cubic centimeter of tenth-normal hydrochloric acid used will correspond to 0.02347 Gm. mercuric oxycyanide ( $\text{Hg}(\text{CN})_2\text{HgO}$ ).

**Mercuric Oxycyanide-Merck.**—A nonproprietary brand complying with the standards for mercuric oxycyanide.

Merck & Co., New York, distributors.



**MERCURIC SALICYLATE.**—Hydrargyrum Salicylicum. For description see the U. S. Pharmacopeia under Hydrargyri Salicylas.

*Actions and Uses.*—Antiseptic and antisypilitic. It has been stated that mercuric salicylate is well tolerated by the stomach and that it does not produce salivation, but it may produce some gastro-intestinal irritation occasionally, even when used intramuscularly. The lack of salivation is probably due to its insolubility and slow absorption and not to any peculiarity of its effects. It is used as a disinfectant and as a remedy in syphilis and in certain skin diseases.

*Dosage.*—From 0.03 to 0.12 Gm. ( $\frac{1}{2}$  to 2 grains). For intramuscular injections a suspension in liquid petrolatum, 1 part in 10, is used; before injecting the mixture must be well shaken in order that the insoluble salt may not remain at the bottom. The needle and syringe should be thoroughly cleansed after each injection, as the insoluble drug readily clogs the instrument. At first, 0.65 Cc. (10 minims) of the mixture described should be injected deeply into the gluteal region every fourth day and this may be increased to every second day if no symptomatic evidences of the action of the drug appear. It is used in the form of dusting powder and ointment (1:10). A suspension in a mucilaginous vehicle (1:300) is used as an injection in gonorrhea, 1 Cc. (15 minims) being injected at a time. As a disinfectant the salicylate is as powerful as mercuric chloride, its great drawback being its insolubility; in order to overcome this difficulty the following formula has been devised: mercuric chloride, 1 part; sodium salicylate, 3 parts; dissolved in distilled water, 100 parts.

*Sterile Ampules of Mercury Salicylate-H. W. & D., 1 grain.*—One Cc. of suspension contains 0.06 Gm. (1 grain) of mercuric salicylate. Each ampule contains more than 1 Cc. of suspension.

*Sterile Ampules of Mercury Salicylate-H. W. & D.,  $1\frac{1}{2}$  grains.*—One Cc. of suspension contains 0.09 Gm. ( $1\frac{1}{2}$  grains) of mercuric salicylate. Each ampule contains more than 1 Cc. of suspension.

*Sterile Ampules of Mercury Salicylate-H. W. & D., 2 grains.*—One Cc. of suspension contains 0.12 Gm. (2 grains) of mercuric salicylate. Each ampule contains more than 1 Cc. of suspension.

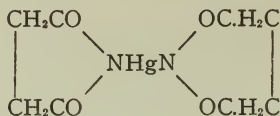
In these ampules mercuric salicylate is suspended in a mixture of vegetable fats which are solid at 34.4 C., but liquid at body temperature. For use the ampules are immersed in warm water until the fat is liquefied, agitated, opened, and a measured quantity of the contents injected through a 20-gauge needle. This preparation should not be injected intravenously.

Prepared by Hynson, Westcott & Dunning, Baltimore, Md.

*Ampuls Mercuric Salicylate-Squibb, 0.065 Gm.*—Each ampule contains mercuric salicylate 0.065 Gm. (1 grain) in 1 Cc. of sterile suspension.

Prepared by E. R. Squibb & Sons, New York.

**MERCURIC SUCCINIMIDE.**—Hydrargyri Succinimidum.  
— $\text{Hg}[(\text{CH}_2\text{CO})_2\text{N}]_2$ .—The mercuric salt of succinic acid-imide,



*Actions and Uses.*—Mercuric succinimide has the action of other salts of mercury, but its solutions are said to be relatively nonirritating. The preparation is used like other compounds of mercury in the treatment of syphilis.

*Dosage.*—Mercuric succinimide is used mainly by hypodermic injection. The daily hypodermic dose is from 0.01 to 0.02 Gm. ( $\frac{1}{6}$  to  $\frac{1}{3}$  grain) given in the form of a 2.5 per cent. solution (from 0.5 to 1 Cc., or 8 to 16 minims of such solution).—Mercuric succinimide may be given by the mouth in doses of from 0.01 to 0.15 Gm. ( $\frac{1}{6}$  to  $\frac{1}{4}$  grain).

*Tabloid Mercury Succinimide (Hypodermic), 1/5 grain.*—Each tablet contains mercuric succinimide 0.013 Gm. (1/5 grain).

Prepared by Burroughs Wellcome & Co., London and New York.

*Ampuls Mercury Succinimide-Mulford, 1/6 grain.*—Each ampule contains mercury succinimide 0.01 Gm. (1/6 grain).

Prepared by H. K. Mulford Co., Philadelphia.

*Hypodermic Tablets Mercuric Succinimide, 1/5 grain.*—Each tablet contains mercuric succinimide 0.013 Gm. (1/5 grain).

Prepared by Sharp & Dohme, Baltimore.

*Hypodermic Tablets Mercuric Succinimide, 1/10 grain.*—Each tablet contains mercuric succinimide 0.006 Gm. (1/10 grain).

Prepared by Sharp & Dohme, Baltimore.

Mercuric succinimide may be prepared by dissolving freshly precipitated mercuric oxide in warm aqueous solution of succinimide and evaporating the mixture, which then deposits crystalline needles. (Schmidt's Pharm. Chemie, 2: Part 1, p. 482). It may also be prepared by adding an alcoholic solution of succinimide containing a few drops of ammonia to an ethereal solution of mercuric chloride (*Proc. Am. Pharm. Assn.*, 40:1029).

Mercuric succinimide is a white crystalline powder, soluble in 25 parts hot water and in 75 parts of cold water, and in 300 parts of alcohol. It is very stable in solution. The aqueous solution is not affected by albumin. Mercuric succinimide should be protected from light. Toward hydrogen sulphide and potassium iodide it reacts as an inorganic mercuric compound. Addition of sodium hydroxide to an aqueous solution of mercuric succinimide produces a yellowish-white precipitate, which on heating is reduced to metallic mercury. If mercuric succinimide is heated with five times its bulk of zinc dust, pyrrol is given off, which may be recognized by the red color which is developed when a pine shaving moistened with hydrochloric acid is held in its vapors.

The aqueous solution must be neutral and should not be affected by solutions of silver nitrate or egg-albumin (absence of mercuric chloride and other mercuric salts).

On ignition it should volatilize completely, leaving no residue. If 1 Gm. is shaken with 10 Cc. of anhydrous ether, the liquid filtered and the ether removed by evaporation, no weighable residue should remain. If 1 Gm. is suspended in ether and hydrogen sulphide passed through the mixture for some time, the mercury succinimide will be decomposed, the mercury being precipitated as mercuric sulphide. If the ether be filtered from this precipitate, and evaporated, a residue of succinimide will remain which should have a melting-point of from 124 to 125 C.

**Mercury Succinimide-Merck.**—A nonproprietary brand complying with the standards for mercuric succinimide.

Merck & Co., New York, distributors.

**MERGAL.**—A mixture of 1 part of mercuric cholate and 2 parts of albumin tannate put up in capsules. Each capsule said to contain approximately 0.15 Gm. ( $2\frac{1}{4}$  grains) of mergal, equivalent to 0.05 Gm. ( $\frac{3}{4}$  grain) mercuric cholate and 0.1 Gm. ( $1\frac{1}{2}$  grains) albumin tannate. Mergal contains approximately 4.4 per cent. mercury.

*Actions and Uses.*—Mergal is said to pass through the stomach without decomposition and to be decomposed into its constituents in the small intestine, where the mercury is quickly absorbed into the blood and excreted through the kidneys. It is said to be useful in all forms of syphilis and in the so-called parasyphilitic affections, such as tabes and general paralysis. It is also said to be useful for the intermittent treatment according to the method of Fournier and Neisser.

*Dosage.*—One capsule three times a day after meals, gradually increasing to 2 capsules five or six times a day.

Manufactured by J. D. Riedel Aktiengesellschaft, Berlin, Germany (Riedel & Co., New York). U. S. patent No. 811,193 (Jan. 30, 1906; expires 1923). U. S. trademark No. 53,919.

Mercuric cholate is prepared by a patented process, mixed with albumin tannate, and inserted into gelatin capsules in the usual way.

Mergal is a yellowish-white, loose, somewhat light powder, insoluble in water and alcohol and almost insoluble in solution of sodium chloride.

When 0.1 Gm. of mergal is shaken with a few drops of saturated solution of cane sugar and underlaid with concentrated sulphuric acid, a purplish red to reddish violet zone is produced. If 0.2 Gm. of mergal is warmed on the water-bath with 10 Cc. of hydrochloric acid for about fifteen minutes and the evaporated water replaced after cooling and filtering, there results a colorless or slightly yellowish solution which gives a black precipitate with solution of hydrogen sulphide. The same filtrate gives with a drop of stannous chloride solution an immediate precipitation of metallic mercury. Mergal should leave no weighable residue on incineration. 0.2 Gm. of mergal boiled for one minute with 20 Cc. of water gives a clear filtrate which is colored dark violet on the addition of a drop of solution of ferric chloride. 0.1 Gm. of mergal when heated with a mixture of 5 Cc. of

concentrated sulphuric acid and 5 Cc. of water to boiling produces a turbid reddish solution. The filtrate after dilution with 3 or 4 parts of water and the addition of a drop of solution of copper sulphate gives on careful underlaying or on mixture with an excess of sodium hydroxide solution an evanescent violet-red color. Mergal should be protected from the light.

**POTASSIUM MERCURIC-IODIDE.**—Potassii Hydrargyro-Iodidum.—A complex salt formed by interaction of mercuric iodide with potassium iodide.

*Actions and Uses.*—The same as those of mercuric iodide, over which this drug is claimed to have some advantages because of its solubility.

When mercuric iodide is added to an excess of potassium iodide solution a colorless liquid is obtained containing the mercuric iodide as a complex salt, approximately  $K_2HgI_4$  (or  $2KI + HgI_2$ ). Under suitable conditions (Naylor and Chappel, *Pharm. Jour.*, March 7, 1908, p. 315) the salt having the composition  $K_2HgI_4 + 3H_2O$  (or  $2KI + HgI_2 + 3H_2O$ ) may be obtained in yellow needle-shaped crystals.

Potassium mercuric-iodide is deliquescent and is decomposed by water.

**Mercury and Potassium Iodide-Merck.**—A nonproprietary brand complying with the standards for potassium mercuric-iodide.

Merck & Co., New York, distributors.

**Soloid Mercuric Potassium Iodide.**—Tablets said to contain in each tablet mercuric potassium iodide (potassium mercuric-iodide)—( $HgI_2 \cdot 2KI = K_2HgI_4$ ) 0.113 Gm. (1.75 grains), an excess of potassium iodide, which prevents the decomposition of the potassium mercuric iodide when water is added, and a trace of coloring matter.

Prepared by Burroughs Wellcome & Co., London, England, and New York.

### Mercurous Compounds

**CALOMELOL.**—Hydrargyri Chloridum Mite Colloidale.—Colloidal Calomel.—A colloidal form of calomel, containing albuminoids.

*Actions and Uses.*—The action of calomelol is the same as that of calomel, but it is claimed to be superior because of its power of forming colloidal suspension in water, acting more rapidly and efficiently, and to be nonirritant. The indications for its use are the same as for calomel.

*Dosage.*—Internally the same as calomel. Externally it is used as a dusting powder, mixed with an equal quantity of starch or of a mixture of starch and zinc oxide, or in the form of calomelol ointment. It should be guarded from the light.



Manufactured by the Heyden Chemical Works, New York. U. S. patent No. 740,855 (Oct. 6, 1902; expires 1920). U. S. trademark.

**Calomelol Ointment.**—Calomelol ointment is an ointment containing 28 per cent. mercury in the soluble form of calomelol (which see) and 2 per cent. in the insoluble form.

It is prepared by combining 45 parts of calomelol with sufficient lard to make 100 parts.

**Dosage.**—6 Gm. (90 grains) daily for inunction in syphilis.

According to the patent, calomelol is prepared by acting on a solution of sodium chloride in presence of a protein with mercurous nitrate and precipitating the colloidal calomel by means of alcohol. The precipitate is washed with alcohol, redissolved in water with the aid of a little alkali, and from this solution the colloidal calomel is obtained either by evaporation or by precipitation with alcohol.

It forms a white-gray, odorless and tasteless powder, containing 80 per cent. of mercurous chloride and 20 per cent. of proteins. With water it forms an opalescent suspension insoluble in alcohol, ether and benzene. (In these suspensions colloidal bodies are in such extreme state of subdivision that they were formerly supposed to be in solution and are still so considered.) It is precipitated from its aqueous suspension by acids, the precipitate being redissolved by alkalis.

### Mercury, Metallic

**ELECTR-HG.**—Electromercurool.—A colloidal suspension of mercury equivalent to 0.1 per cent. metallic mercury (Hg) and containing a small percentage of sodium arabate.

**Actions and Uses.**—Electr-Hg is claimed to have an action similar to that of the soluble salts of mercury. Locally it is said to produce no pain when given by intramuscular injection, and to leave no induration.

**Dosage.**—It is injected intramuscularly and intravenously in doses of 5 Cc. per day. For the intraspinal injection the dose is from 1 to 2 Cc., injected once a month or less frequently according to the effects it produces.

Electr-Hg is marketed in ampules only, in a nonisotonized condition. The package contains a physiologic salt solution with directions for the extemporaneous isotonzation of the preparation before the injection.

Manufactured by Comar & Cie., Paris, France (E. Fougere & Co., New York). No U. S. patent. U. S. trademark No. 110,568.

**Ampoules Electr-Hg, 5 Cc.**—Each ampule contains electr-Hg 5 Cc. (75 minims).

Electr-Hg is prepared by passing an electric current in the form of an arc between two mercury electrodes in distilled water. It is made stable by the addition of sodium arabate, which is prepared by acting on acacia (gum arabic) with hydrochloric acid, precipitating the resulting arabic acid with alcohol and neutralizing the arabic acid with sodium carbonate.

Electr-Hg is an odorless, tasteless liquid appearing transparent and brown in color by transmitted light and opaque and gray by reflected light. The addition of potassium cyanide solution or of strong nitric acid yields clear, colorless solutions. The nitric acid solution responds to tests for mercury.

**MERCURIAL OIL.**—Grey Oil.—A mixture containing from 40 to 50 per cent. metallic mercury in an oil base containing the mercury in a finely divided state and of a consistence which permits its intramuscular injection by means of a proper syringe at room temperature.

*Actions and Uses.*—Mercurial oil is used by intramuscular injection as a means of obtaining the systemic effects of mercury. It is believed by some that the rate of absorption is influenced by the size of the mercury globules; hence the degree of subdivision should be indicated for each brand of this product.

*Dosage.*—Depending on the effects desired, the mercurial oil is administered once or twice a week, 0.06 Cc. (1 minim being the initial dose and 0.12 Cc. (2 minims) the maximum. The "course" should not be continued beyond five or six weeks, without an intermission of equal duration. It is reported that cumulative effects are prone to develop from the use of mercurial oil. Idiosyncrasy should be considered and salivation must be carefully watched for. Tenderness of the gums (the earliest sign of salivation) is an indication for stopping the use of the drug for a period.

In mercurial oil the globules of mercury tend to coalesce and form larger globules, and when this process is once started it progresses very rapidly. Mercurial oil should be kept at a relatively constant temperature and must not be warmed prior to use.

**Mercurial Oil-National Pathological Laboratory.**—A mixture of equal weights of mercury and lanolin obtained by triturating the constituents until mercury globules are no longer macroscopically visible. It is marketed in graduated syringes ready for use and containing 2 Cc. Syringes containing visible mercury globules should be discarded.

National Pathological Laboratory, Chicago.

**MERCURIAL OINTMENT, IMPROVED-Mulford.**—An ointment containing 50 per cent. of metallic mercury in an ointment base consisting of anhydrous wool-fat, petrolatum and suet, aromatized.

*Actions and Uses.*—The same as those of mercurial ointment, U. S. P. Mercurial ointment, improved, is devoid of the unpleasant odor of mercurial ointment, U. S. P., and is claimed to be more readily absorbed.

*Dosage.*—The same as that of mercurial ointment, U. S. P.

Manufactured by the H. K. Mulford Co., Philadelphia. No U. S. patent or trademark.

*Capsules Mercurial Ointment, Improved-Mulford, 30 grains.*—Each capsule contains mercurial ointment, improved, Mulford, 2 Gm. (30 grains).

*Capsules Mercurial Ointment, Improved-Mulford, 60 grains.*—Each capsule contains mercurial ointment, improved, Mulford, 4 Gm. (60 grains).

Mercurial ointment, improved, is a slate-colored, semisolid mass, having a pleasant, aromatic odor.

## NAPHTHOL COMPOUNDS

Compounds of naphthol that are insoluble in the stomach have been introduced in therapeutics. The expectation has been that, owing to the greater concentration of the naphthol in the intestines after its liberation by the bile and pancreatic juices, these compounds would have a maximum antiseptic action. In addition, the action of whatever substance was united with the naphthol would be exerted, whether on the intestine or some other part of the body, such as the genito-urinary tract.

A wide difference of opinion, however, exists among authorities as to the actual efficiency of all intestinal antiseptics and of most urinary antiseptics. Whatever opinion regarding this is followed, it should be remembered that if used freely or for a long time any of them may have irritating effects on the digestive tract or undesirable effects on other tissues. Reasonable caution should therefore be exercised in using them.

**BETANAPHTHYL BENZOATE.**—Betanaphtholis Benzoas.—Betanaphthol Benzoate.—Benzonaphthol.— $C_6H_5COO$ . ( $C_{10}H_7$ ). The benzoic ester of betanaphthol.

*Actions and Uses.*—Betanaphthyl benzoate is not decomposed by the gastric fluid, but is split into its constituents in the intestinal canal.

Betanaphthyl benzoate is used internally as an intestinal antiseptic in diarrhea and typhoid fever. Externally betanaphthyl benzoate is used as a parasiticide in the form of 3 to 10 per cent. ointment, and has been used in psoriasis, eczema, scabies, etc.

*Dosage.*—From 0.2 to 0.5 Gm. (3 to 8 grains); maximum dose, single, 1 Gm. (15 grains) daily 4 Gm. (60 grains).

Betanaphthyl benzoate may be obtained by heating betanaphthol and benzoyl chloride together at 170 C., extracting the resulting product with alcohol and purifying by crystallization.

Betanaphthyl benzoate occurs in colorless needles or as a white crystalline powder, tasteless and melting at 107 to 110 C.

Betanaphthyl benzoate is almost insoluble in water, but very soluble in alcohol and ether; also soluble in chloroform and fixed oils.

Betanaphthyl benzoate heated with a solution of potassium hydroxide in alcohol develops the odor of ethyl benzoate; on the addition of chloroform the mixture acquires a blue color.

Incinerate 0.5 Gm. betanaphthyl benzoate; not more than 0.1 per cent. of ash remains.

Shake vigorously for one minute 1 Gm. of betanaphthyl benzoate with 20 Cc. of a cold 5 per cent. aqueous sodium hydroxide solution and immediately filter. To 10 Cc. of the filtrate add 2 Cc. of chloroform and boil; no blue color is produced in the aqueous layer (*uncombined betanaphthol*). Carefully neutralize the remaining 10 Cc. of the alkaline filtrate, then add a few drops of ferric chloride test solution previously diluted with two volumes of distilled water and neutralize, if necessary, with ammonia water; no pink precipitate is produced (*uncombined benzoic acid*).

Shake vigorously for one minute 0.5 Gm. betanaphthyl benzoate with 5 Cc. of an aqueous 5 per cent. sodium hydroxide solution and filter. No blue color develops in the filtrate on the addition of a few drops of iodine test solution (*alphanaphthol*).

Shake vigorously for one minute 0.5 Gm. betanaphthyl benzoate with 50 Cc. distilled water and filter. The filtrate should not be acid toward litmus. Five Cc. portions of the filtrate mixed with equal volumes of diluted nitric acid do not become turbid on the addition of 1 Cc. silver nitrate test solution (*chloride*) or barium nitrate test solution (*sulphate*).

Betanaphthyl benzoate is incompatible with antipyrine, camphor, phenol, ferric chloride, menthol, potassium permanganate, or ethyl carbonate.

**Betanaphthol Benzoate—Anthony-Hammond Chemical Works, Inc.**—A nonproprietary brand complying with standards for betanaphthol benzoate.

Manufactured by Anthony-Hammond Chemical Works, Inc., New York City.

**Betanaphthol Benzoate-Calco.**—A nonproprietary brand complying with the standards for betanaphthol benzoate.

Manufactured by The Calco Chemical Company, Bound Brook, N. J.

**Betanaphthol Benzoate-Merck.**—A nonproprietary brand complying with the standards for betanaphthol benzoate.

Merck & Co., New York, distributors. No U. S. patent or trademark.

**Betanaphthol Benzoate-Roche.**—A nonproprietary brand complying with the standards for betanaphthol benzoate.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York).

**BETANAPHTHYL SALICYLATE.** — Betanaphtholis Salicylas.— $C_{10}H_7.OH.CO.O.(C_{10}H_7)$ .—The salicylic acid ester of betanaphthol.

**Actions and Uses.**—Betanaphthyl salicylate undergoes no change in the stomach, but is split up into its original compounds when it reaches the intestinal tract by the pancreatic juice and intestinal secretions. It is believed to act as an intestinal antiseptic and, being excreted in the urine, to act in a similar way in the bladder. (See preceding general article on Naphthol Compounds).



It has the antirheumatic properties of salicylic acid. It is said to be useful in intestinal fermentations, catarrh of the bladder, particularly gonorrheal cystitis, rheumatism, etc.

*Dosage.*—From 0.3 to 0.5 Gm. (4 to 8 grains) in cachets, milk or emulsion.

Betanaphthyl salicylate is obtained by heating betanaphthyl-sodium and sodium salicylate with phosphorus oxychloride at from 120 to 130 C.

It is a white lustrous crystalline powder, colorless and tasteless, melting between 93 and 95 C. It is insoluble in cold or hot water or glycerin, soluble with difficulty in cold alcohol or turpentine, easily soluble in boiling alcohol, in ether, in benzene, and in war linseed oil. In the cold it is not changed by acids or alkalies of moderate concentration. When heated with alkalies it is decomposed into its constituents, which, if the solution be acidulated, will crystallize.

It is distinguished from salol by its higher melting-point and by the production of a brownish-green color, when a trace of nitric acid is added to its yellow colored solution in pure sulphuric acid. It burns on platinum foil, leaving no residue (*fixed mineral impurities*). If 1 Gm. of betanaphthyl salicylate be shaken with 30 Gm. of boiling water and filtered through a moistened filter, the filtrate should not have an acid reaction (*salicylic, hydrochloric or phosphoric acid*), nor should it after cooling show a crystalline deposit (*salicylic acid or betanaphthol*); nor should it become turbid on the addition of silver nitrate (*chlorides or phosphates*) or barium nitrate (*sulphate*), nor should it give a violet color with solution of ferric chloride.

**Betanaphthyl Salicylate-Calco.**—A brand of betanaphthyl salicylate.

Manufactured by the Calco Chemical Company, Bound Brook, N. J. No U. S. patent or trademark.

**Betanaphthyl Salicylate-M. C. W.**—A betanaphthyl salicylate.

Manufactured by the Mallinckrodt Chemical Works, St. Louis, Mo.

**BISMUTH BETANAPHTHOLATE.** — See Bismuth Compounds, Insoluble.

## NITRATES—ORGANIC

The esters of nitric acid and the higher alcohols (glycerin, propane-triol), erythrite (butane-tetrol), etc., have an action on the blood vessels similar to that of the inorganic nitrites (sodium nitrite) and that of the nitrous acid esters of the alcohols (amyl nitrite, ethyl nitrite); this is generally attributed to the formation from them, in the body, of nitrites. The action of organic nitrates differs from that of the organic nitrites chiefly in that the action of the former is longer continued; this is seen in the case of glyceryl trinitrate, U.S.P. (nitroglycerin), and, to a still greater degree, in the following:

**ERYTHROL TETRANITRATE.**—Tetranitrol— $C_4H_6(NO_3)_4$ .—The tetranitrate of erythrite (butane-tetrol),  $C_4H_6(OH)_4$ .

*Actions and Uses.*—Erythrol tetranitrate is a vasodilator like nitroglycerin. Its action is slower and more lasting; it begins in fifteen minutes and persists for three or four hours.

It is said to be useful in angina pectoris and vascular diseases. It is reported as especially useful as a prophylactic in preventing anginal pain.

*Dosage*—From 0.03 to 0.06 Gm. ( $\frac{1}{2}$  to 1 grain) every four to six hours. Like nitroglycerin and many similar organic nitrates, it is a violent explosive; it is dispensed only in tablets. Sold in the form of tablets only.

Merck & Co., New York, distributors. German patent No. 81,664.

*Erythrol Tetranitrate Tablets-Merck.*—Each tablet contains erythrol tetranitrate 0.03 Gm. ( $\frac{1}{2}$  grain).

Erythrol tetranitrate is obtained by the nitration of the tetratomic alcohol erythrite.

It forms colorless crystalline scales, insoluble in cold water, readily soluble in alcohol, melting at 61 C. On percussion it explodes much like nitroglycerin.

## NUCLEINS AND NUCLEIC ACIDS

The nucleins are complex combinations of a protein group, acting as a base, with a nucleic acid; but less complex than are the original nucleoproteins from which they are derived by treatment with alkali or by partial digestion.

The term "nuclein" is very carelessly employed, being often used where nucleic acid is meant. The composition of nucleins, as they appear in commerce, varies according to the process employed in their manufacture. By prolonged or stronger treatment the composition of nuclein tends to approach more and more to that of the nucleic acid residue through the elimination of more and more of the protein group in combination. The nucleic acids, on the other hand, are definite chemical compounds of very complex structure. Several of them have been obtained from nucleoproteins of vegetable and animal origin. The best known are from the wheat embryo, yeast, the pancreas and thymus glands and certain fishes' sperm. Cells, in general, are rich in nucleoproteins.

The processes of isolation are rather complicated; in the extraction from tissues the following general scheme has been employed: The finely ground organs are digested at a boiling heat with sodium hydroxide solution of about 2 per cent. strength containing 10 per cent. of sodium acetate. After one hour's digestion the mixture is filtered hot. After concentration the filtrate is neutralized with acetic acid, which does not precipitate the ordinary nucleic acids, and filtered again. The new filtrate is precipitated by alcohol and the crude salts

obtained purified by washing with alcohol. Finally the salts are dissolved in hot water and decomposed by dilute hydrochloric acid, which throws down the free nucleic acids.

Nucleic acids are practically insoluble in water, alcohol, ether or other organic solvents. The alkali salts are soluble in water and especially in presence of sodium acetate. The salts of the heavy metals are insoluble. The pure acids do not give the biuret reaction or the reaction with Millon's reagent, but the so-called nucleins give these and other tests because of the presence of protein residues. On complete hydrolysis nucleic acids yield a carbohydrate group, purine and pyrimidine bases, and phosphoric acid. The following formulas show with a considerable degree of accuracy the composition of nucleic acids from different sources:

$C_{40}H_{56}O_{26}N_{14}P_4$	From thymus glands
$C_{40}H_{56}O_{26}N_{14}P_4$	salmon milt
$C_{41}H_{61}O_{31}N_{16}P_4$	wheat embryo
$C_{36}H_{45}O_{30}N_{14}P_4$	yeast cells

A close approximation to the structural formula has been worked out for several of these acids.

*Actions and Uses.*—Some years ago these acids and the nucleins were introduced as remedies in tuberculosis, and to a slight extent this use continues. It has been held that their administration increases the number of white corpuscles and in consequence becomes of value in treating infections. The evidence on which these claims are based, however, is neither clear nor convincing. In the organism the metabolism of the nucleic acids yields purine bases and phosphoric acid.

As the purine derivatives of nucleic acids are the more common precursors of uric acid the importance of the nucleins with reference to gout must not be overlooked. Ordinary lean meats contain but small amounts of nucleoproteins, but in the kidney, liver, sweetbreads, brains and some other foods they are more or less abundantly present. Under some conditions, therefore, such foods are to be avoided.

**NUCLEIN.** — *Nucleinum.* — A modified nucleoprotein obtained by peptic digestion or by treatment with dilute acids.

*Actions and Uses.*—See preceding general article, Nucleins and Nucleic Acids.

*Dosage.*—From 0.5 to 1 Gm. (8 to 15 grains) three times a day.

**NUCLEIC ACID.**—*Acidum Nucleicum.*—Nucleinic Acid.—An organic acid obtained from nuclein by the action of alkalis or by tryptic digestion.

*Actions and Uses.*—See preceding general article, Nucleins and Nucleic Acids.

*Dosage.*—From 0.06 to 0.03 Gm. (1 to 5 grains) three times a day.

Nucleic acid is an amorphous, white powder and has an acid reaction. It is readily soluble in ammoniacal or alkaline water with the formation of water-soluble salts. From these solutions it is precipitated by slight excess of hydrochloric acid but not by acetic acid. It is insoluble in alcohol and ether. When chemically pure it does not give the biuret test or Millon's reaction, but a slight response to these reagents does not indicate a degree of impurity incompatible with its use as a medicinal agent.

It should contain between 14.5 and 16.5 per cent. of nitrogen and between 8.5 and 10.5 per cent. of phosphorus, the relative proportions being 4 atoms of P. to 14 or 16 N., approximately.

**Nucleinic Acid-Merck** (from yeast).—A nonproprietary brand complying with the standards for nucleic acid.

Merck & Co., New York, distributors.

**SODIUM NUCLEATE.**—Sodii Nucleas.—Sodium Nucleinate.—The sodium salt of nucleic acid.

*Actions and Uses.*—See preceding general article, Nucleins and Nucleic Acids.

*Dosage.*—Practically the same as that of nucleic acid.

**Nuclein-Abbott.**—Sodium Tritico-Nucleinate-Abbott. — A sodium nucleate derived from the wheat germ.

Manufactured by the Abbott Laboratories, Chicago. No U. S. patent or trademark.

*Nuclein Solution-Abbott.*—Liquor Sodii Tritico-Nucleinatis-Abbott.—A solution of nuclein-Abbott containing approximately 10 Gm. of the salt in 100 Cc. (6 grains) in one fluidrachm of a menstruum containing 15 per cent. of alcohol. The solution is standardized to contain 1 mg. phosphorus in 1 Cc.

The aqueous extract of the wheat germ is treated with sodium chloride and acid, the precipitate digested with pepsin, neutralized with sodium hydroxide and purified by precipitation with alcohol. The resulting sodium tritico-nucleinate is dissolved in distilled water and 15 per cent. of alcohol as a preservative.

*Nuclein Tablets-Abbott.*—Each tablet is said to contain 0.13 Cc. (2 minims) of nuclein solution-Abbott.

Nuclein-Abbott is a grayish-white powder, soluble in water and insoluble in alcohol. On incineration it yields approximately 26 per cent. of ash, which is slightly alkaline and readily soluble in water. It contains phosphorus and nitrogen in the ratio of 1 atom of P to 3.66 N. When the aqueous solution is decomposed by weak hydrochloric acid, a voluminous precipitate of the free nucleic acid is formed.

**Sodium Nucleinate-Merck.**—A nonproprietary brand complying with the standards for sodium nucleate.

Merck & Co., New York, distributors.



## OPIUM PRINCIPLES, DERIVATIVES AND PREPARATIONS

Morphine is a complex derivative of phenanthrene. It contains two OH groups (one phenolic, the other alcoholic) in which substitutions can be made by either alkyl or acid radicals.

The more important alkyl esters are the monomethyl (codeine); the dimethyl (thebaine); and ethyl-morphine. Heroin is the diacetyl derivative.

The nature of these radicals—whether acid or alcoholic, aromatic or aliphatic—modifies the actions, quantitatively, but only in a minor degree. Replacement of one hydroxyl group (codeine) diminishes the narcotic action and increases the respiratory and tetanic action. When both OH groups are replaced by acids (heroin) the narcotic effects are stronger than with codeine, and the tetanic action is weaker than with morphine.

*Actions and Uses.*—The central actions of all these morphine derivatives are qualitatively identical; but they present quantitative differences which have some practical importance:

*Morphine* produces the strongest narcotic, analgesic, hypnotic and intestinal effects, and the weakest stimulation. It causes the greatest derangement of digestion. It and diacetyl morphine (heroin) are most apt to induce a habit.

*Codeine* (methyl-morphine) is less narcotic, less constipating, and less apt to induce tolerance and habit. It is therefore especially valuable in cough or in other conditions in which the sedative action must be continued for some time and in patients who do not tolerate morphine. (See also Codeine Derivatives.)

*Ethyl-Morphine* seems to stand intermediate between morphine and codeine, in all respects. The hydrochlorid is being used as a sedative; but mainly for its special action on the conjunctivae (see below).

*Diacetyl-Morphine* (heroin) approaches very closely to morphine, of which it shares all the disadvantages, and over which it has no important advantage.

It was originally introduced with the claim that therapeutic doses lessen the cough reflex and slow the respiration; but that the inspirations are deepened and more powerful, so that the alveolar air is more effectively ventilated. Independent workers, however, have shown that there is no real difference from morphine in these respects. It is now generally conceded that diacetyl-morphine is as effective as morphine in cough, but not more so; that it is rather less effective against dyspnea; and that it is more liable to produce habit and toxic effects. Codeine seems to be superior to heroin in its power to allay cough, to overcome pain and to promote sleep (Bastedo).

**DIACETYL-MORPHINE.**—For description see the U. S. Pharmacopeia under Diacetylmorphina.

**Heroin.**—A proprietary name applied to diacetyl-morphine.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. trademark No. 31,836.

**DIACETYL-MORPHINE HYDROCHLORIDE.**—For description see the U. S. Pharmacopeia under Diacetylmorphinae Hydrochloridum.

*Actions and Uses.*—See Useful Drugs.

**Heroin Hydrochloride.**—A proprietary name applied to diacetyl-morphine hydrochloride.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. trademark No. 31,836.

**ETHYL-MORPHINE HYDROCHLORIDE.**—For description see the U. S. Pharmacopeia under Aethylmorphinae Hydrochloridum.

*Actions, Uses and Dosage.*—See Useful Drugs.

**MORPHINE MECONATE.**—Morphinae Meconas.— $(C_{17}H_{19}O_3N)_2 \cdot C_7H_4O_7 + 5H_2O$ .—The normal salt of morphine,  $C_{17}H_{19}O_3N$ , and meconic acid,  $H_2(C_7H_4O_7)$ , a dibasic acid obtained from opium.

*Actions, Uses and Dosage.*—The same as those of other salts of morphine.

*Tabloid Morphine Meconate (Hypodermic) 1/8 grain.*—Each tablet contains morphine meconate 0.008 Gm. ( $\frac{1}{8}$  grain). Prepared by Burroughs Wellcome & Co., London, England, and New York.

Morphine meconate may be prepared by dissolving 10 Gm. crystallized meconic acid in 60 Cc. warm water, adding gradually 24 Gm., or sufficient crystallized morphine alkaloid to produce a neutral solution and evaporating to dryness at a temperature below 80 C. (Hager, 2: 403, 1903.)

Morphine meconate occurs in minute colorless crystals or a yellowish-white powder, soluble in 34 parts of water, also soluble in alcohol. Theoretically, morphine meconate contains 66.3 per cent. anhydrous morphine.

**Morphine Meconate-Merck.**—A nonproprietary brand complying with the standards for morphine meconate.

Merck & Co., New York, distributors.

**PANTOPON-ROCHE.**—Pantopium Hydrochloricum.—A mixture of the hydrochlorides of the alkaloids of opium in

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the proportion in which they exist in Smyrna opium, containing 50 per cent. of anhydrous morphine hydrochloride.

*Actions and Uses.*—Pantopon-Roche (pantopium hydrochloricum) produces essentially the effects of opium, but, being devoid of its extractive it may be used for hypodermic administration. It is probably absorbed rather more promptly, and is free from the nauseant odor and taste of the ordinary opium preparations. It is used in the same conditions as those in which opium is indicated.

*Dosage.*—For adults, 0.005 to 0.02 Gm. ( $\frac{1}{12}$  to  $\frac{1}{3}$  grain) hypodermically or by mouth. One grain of pantopon-Roche (pantopium hydrochloricum) is equivalent to:

2½ grains of extract of opium, U. S. P.

5 grains of powdered opium, U. S. P.

45 minims of tincture of opium, U. S. P.

$\frac{9}{10}$  grain of morphine sulphate, U. S. P.

Manufactured by F. Hoffmann-LaRoche and Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York). U. S. patent No. 1,056,219 (March 18, 1913; expires 1930). U. S. trademark No. 77,371.

*Pantopon-Roche (Pantopium Hydrochloricum) Tablets.*—Each tablet contains pantopon-Roche (pantopium hydrochloricum) 0.01 Gm.

*Pantopon-Roche (Pantopium Hydrochloricum) Hypodermic Tablets.*—Each tablet contains pantopon-Roche (pantopium hydrochloricum) 0.02 Gm.

*Pantopon-Roche (Pantopium Hydrochloricum) Ampules for Hypodermic Administration.*—One Cc. of solution contains 0.02 Gm. pantopon-Roche (pantopium hydrochloricum). Each ampule contains 1.1 Cc. sterile solution.

Pantopon-Roche (pantopium hydrochloricum) is a yellowish-gray crystalline powder which is readily soluble in water.

If a few drops of ammonia water be added to an aqueous solution of pantopon-Roche (pantopium hydrochloricum) (1:200) a precipitate of the secondary opium alkaloids should form at once (distinction from pure *morphine hydrochloride*).

If from 0.5 to 1 Gm. of pantopon-Roche (pantopium hydrochloricum) be weighed and dried at 100 Cc. to constant weight, the loss should correspond to from 9 to 9.5 per cent. of the weight taken.

If from 0.5 to 1 Gm. of pantopon-Roche (pantopium hydrochloricum) be weighed, dissolved in water containing a little nitric acid, the hydrochloric acid determined by precipitation with silver nitrate and weighing the precipitate in the usual way, the silver chlorid found should correspond to between 9.8 per cent. and 10.2 per cent. of hydrochloric acid (HCl).

If 0.8 Gm. of pantopon-Roche (pantopium hydrochloricum) be dissolved in sufficient water to make 40 Gm. of solution, 2 Gm. of normal ammonia water added, the solutions mixed by circulatory rotation (not by shaking), the solution immediately filtered through a dry filter, and 36.75 Gm. of the filtrate (equivalent to 0.7 Gm. of pantopon-Roche (pantopium hydrochloricum) be treated with 10 Cc. of ether and 4 Cc. of normal ammonia water and the assay process completed as described in the Swiss Pharmacopeia, Ed. 4, p. 344, for opium, the tenth-normal hydrochloric acid consumed should correspond to from 44 to 45 per cent. of anhydrous morphine.

**PAPAVERINE.** — Papaverina. —  $C_{20}H_{21}O_4N$ . — An alkaloid obtained from opium, belonging to the benzyl iso-quinoline group (i. e., it is not a morphine derivative).

*Actions and Uses.* — Pal found that papaverine relaxes smooth muscle in general, although different organs are affected in a varying degree.

Papaverine is most effective in hypertonic conditions, while it does not interfere materially with the normal movements, for instance, of the intestines. It is also a rather feeble central analgesic and a local anesthetic. Its toxicity is low, and neither tolerance nor habituation has been reported. These actions have prompted its use, with reported success, in various spasmodic conditions of the smooth muscles. Pal recommends it especially in all kinds of gastric and intestinal spasms (also for the diagnosis of pyloric spasm); in biliary colic; and in bronchial spasm. Of more doubtful value is its employment in pertussis, hyperemesis, and vascular spasm—angina pectoris, acute uremia and eclampsia. It is admitted to be ineffective in chronic hypertonus. The local anesthetic action, with vasodilatation, has been used against rhino-asthma, and to mitigate the pain of irritant injections.

*Dosage.*—The oral and hypodermic single dose is 0.03 to 0.08 Gm. ( $\frac{1}{2}$  to  $1\frac{1}{2}$  grain); daily dose to 0.5 Gm. Single doses of even 1 Gm. are said to be non-toxic.

Papaverine occurs in fine, white rhombic prisms or needles or sometimes in scales; odorless and tasteless.

Papaverine is nearly insoluble in cold water; very sparingly soluble in alcohol, ether, chloroform and benzene if cold; somewhat more soluble in these liquids when hot, but deposited by them on cooling; soluble in warm petroleum ether and in acetone.

Papaverine melts at 147 C.

If about 0.01 Gm. of papaverine be dissolved in 10 Cc. of water containing a few drops of diluted hydrochloric acid, and a few drops of potassium ferricyanide solution added, a lemon-yellow precipitate of papaverine ferricyanide should form at once (distinction from *other opium alkaloids*).

If about 0.001 Gm. of papaverine be dissolved in 0.1 Cc. of sulphuric acid containing in each Cc. 1 drop of formaldehyde solution, a colorless solution, or at most a faintly yellowish-green color, should be produced; this gradually changes to deep rose and finally becomes brown (distinction from *morphine and its esters*, which give purple or violet colors).

If 0.01 Gm. of papaverine be dissolved in 0.2 Cc. of sulphuric acid the solution should not be colored more than very faintly pinkish or brownish (limit of *cryptopine, thebaine or of other organic impurities*).

If 0.01 Gm. of papaverine be dissolved in 10 Cc. of water containing a few drops of hydrochloric acid, a few drops of a saturated aqueous solution of iodic acid added, and the mixture shaken with chloroform, the chloroform layer should not be colored violet (*morphine*).

If from 0.2 to 0.3 Gm. of papaverine be weighed, dissolved in 20 Cc. of warm water containing a few drops of diluted hydrochloric



acid, the solution cooled, 1 Cc. of freshly prepared potassium ferri-cyanide solution added, the mixture agitated, allowed to stand over night, filtered, the filtrate made alkaline with ammonia water, shaken with several successive portions of ether, the ether solutions combined, washed with water, evaporated, the residue dried at 100 C. and weighed, the weight should not amount to more than 2 per cent. of the weight taken (limit of *foreign opium alkaloids*).

**PAPAVERINE HYDROCHLORIDE.**—*Papaverinae Hydrochloridum.*— $C_{20}H_{21}O_4N.H.Cl.$ —The hydrochloride of the alkaloid papaverine, containing not less than 88 per cent. of papaverine.

*Actions, Uses and Dosage.*—See Papaverine.

Papaverine hydrochloride occurs in a fine white, crystalline powder or in small monoclinic plates or prisms; odorless and having a bitter taste; permanent in the air.

Papaverine hydrochloride is sparingly soluble in water; soluble in alcohol; very soluble in chloroform; insoluble in ether.

An aqueous solution of papaverine hydrochloride has an acid reaction toward litmus paper.

If from 0.2 to 0.3 Gm. of papaverine hydrochloride be weighed, dissolved in 20 Cc. of warm water, the solution cooled, a slight excess of ammonia water added and the mixture shaken with 3 successive portions of 25 Cc. each of ether, or a sufficient quantity to complete the extraction, the ether solutions combined, washed with water, evaporated to dryness, the residue dried to constant weight at 100 C. and weighed, the weight should indicate not less than 88 per cent. of papaverine. The alkaloid obtained by this process should conform to the tests for identity and purity described under Papaverine.

**Papaverine Hydrochloride-Merck.**—A nonproprietary brand complying with the standards for papaverine hydrochloride.

Merck & Co., New York, distributors.

**Papaverine Hydrochloride-Roche.**—A nonproprietary brand complying with the standards for papaverine hydrochloride.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche Chemical Works, New York).

*Papaverine Hydrochloride-Roche, Tablets.*—Each tablet contains papaverine hydrochloride, 0.04 Gm.

**PAPAVERINE SULPHATE.**—*Papaverinæ Sulphas.*— $(C_{20}H_{21}O_4N)_2H_2SO_4.$ —The sulphate of the alkaloid papaverine, containing not less than 85 per cent. of papaverine.

*Actions, Uses and Dosage.*—See Papaverine.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche Chemical Works, New York).

*Papaverine Sulphate-Roche, Ampules.*—One Cc. of solution contains 0.04 Gm. papaverine sulphate. Each ampule contains 1.1 Cc. of solution.

Papaverine sulphate occurs in white, crystalline powder; odorless and having a bitter taste; slightly hygroscopic.

Papaverine sulphate is soluble in water and in alcohol; very soluble in chloroform; insoluble in ether.

An aqueous solution of papaverine sulphate has an acid reaction toward litmus paper.

If from 0.2 to 0.3 Gm. of papaverine sulphate be weighed, dissolved in 20 Cc. of water, a slight excess of ammonia water added and the mixture shaken with three successive portions of 25 Cc. each of ether, or a sufficient quantity to complete the extraction, the ether solutions combined, washed with water, evaporated to dryness, the residue dried to constant weight at 100 C. and weighed, the weight should indicate not less than 85 per cent. of papaverine. The alkaloid obtained by this process should conform to the tests for identity and purity described under Papaverine.

## ORGANS OF ANIMALS

The discovery of the importance of internal secretions has led to extensive clinical trials with preparations of the so-called ductless glands, and other tissues which elaborate, or are supposed to elaborate, such internal secretions. Three of these, the thyroid and suprarenal glands and the posterior lobe of the pituitary, have given decisive therapeutic results; these are official in the Pharmacopeia; preparations of the active principle of the suprarenal are described in this book under the heading of "Epinephrine." Pituitary extract has also won a recognized place in therapeutics. The other organ products are scarcely beyond the experimental stage, and may therefore be described together. Their active principles have not been isolated, and they are most commonly used in the form of the powdered dried gland. The gross fat and connective tissue should be removed as completely as possible, and the drying should be conducted at a relatively low temperature. The powder (often improperly called an "extract") is frequently compressed into tablets. It is recommended that the strength of these should be stated in terms of the dried gland. Since there are no tests for the quality, or even identity, of these powdered products, the physician, unless he can himself supervise their preparation, is forced to rely on the general reputation of the manufacturer.

After the description of each gland a list of such preparations as have been submitted to the Council and are being marketed in an unobjectionable manner, is given. For the reasons stated, however, the Council disclaims any responsibility for their quality or identity.

### Leukocytes

**LEUKOCYTE EXTRACT.**—An extract of the leukocytes obtained from exudates produced in the pleural cavities of rabbits or other animals by the injection of an irritant.

*Actions and Uses.*—Leukocyte extract is believed to increase the immunizing power of the organism into which it is injected.

It is said to be useful as an aid to the action of specific serums or antitoxins and vaccines.

It is claimed to be useful by itself in cases in which the correct bacteriologic diagnosis of the infection cannot be obtained. Its use is still in the experimental stage.

*Dosage.*—The extract is injected subcutaneously under strict aseptic precautions. The dose may be repeated daily or less often as indicated by the response after injection.

Leukocyte extract is prepared by inciting an exudate in the pleural cavities of rabbits or other animals through the injection of sterile vegetable protein solution.

After the exudate has collected in sufficient quantities, it is aspirated under strict aseptic precautions from the pleural cavities. It is centrifuged and extracts are made of the leukocyte sediment after determining that the exudate is free from bacteria.

**LEUCOCYTE EXTRACT-SQUIBB.**—A leukocyte extract prepared according to the method of Hiss.

*Dosage.*—Not less than 10 Cc. leucocyte extract-Squibb is furnished in syringes containing 10 Cc.

Manufactured by E. R. Squibb & Sons, New York.

It is claimed that biologic and clinical tests have proved leucocyte extract-Squibb to be of high potency and efficiency.

## Mammary Gland

The extracts of the mammary gland are said to have an effect on the uterus. It is stated that they are useful in the profuse menstruation of young girls and young women and in menorrhagia occurring at the time of the menopause.

**MAMMARY SUBSTANCE-ARMOUR.**—The mammary gland of the sheep freed from fat, cleaned, dried and powdered, without the addition of preservative or diluent.

*Actions and Uses.*—See Mammary Gland.

*Dosage.*—From 0.13 to 0.3 Gm. (2 to 5 grains) three times daily.

Manufactured by Armour & Co., Chicago. No U. S. patent or trademark.

*Mammary Substance Tablets-Armour.*—Each tablet contains desiccated mammary substance 0.13 Gm. (2 grains).

*Dose.*—From 1 to 3 tablets three times a day.

A yellowish to orange-colored powder, having a slight peculiar odor; only partially soluble in water.

One part represents approximately  $4\frac{1}{2}$  parts of the fresh mammary gland of the sheep. It contains nucleoprotein which, when treated with dilute sulphuric acid, yields guanin. (S. Fränkel, *Descriptive Biochemie*, p. 386). On incineration it should not yield more than 9 per cent. ash.

## Ovary

The ovaries produce internal secretions which are necessary for the proper functioning of the uterus and which also have obscure effects on metabolism and the nervous system. Diminution or cessation of the activity of the ovaries (as at menopause, natural or artificial) often leads to a variety of nervous symptoms; irregularities in their activities seem sometimes to be accompanied by dysmenorrhea.

It is generally recognized that one or more of the important internal secretions of the ovaries originate in the corpora lutea and the latter have been tried for the same indications for which the entire gland has been used. It is too early to state whether the two preparations are equivalent, or which is superior.

Ovarian therapy is still on trial. Ovarian substance as well as corpus luteum has been administered, often with apparently good results, for the relief of symptoms following the natural or artificial menopause and in dysmenorrhea, intermenstrual pain, etc. The best results have been obtained in cases of postoperative menopause, especially in young women. Various disturbances of the skin (acne, eczema and prurigo) occurring during the menopause are said to be benefited by it.

The use of corpus luteum has been suggested in obesity associated with amenorrhea and in other conditions of "ovarian insufficiency"; Fränkel states that the drug has no effect in dysmenorrhea, irregular menstruation and the intoxication of pregnancy. Toxic effects, consisting chiefly of nausea and vomiting, have been reported from the administration of preparations of corpus luteum. It has been suggested that the vomiting of pregnancy may be due in part to a deficient activity of the corpus luteum, or to an overactivity of the latter. However, the use of corpus luteum extracts in the vomiting of pregnancy is not based upon either sound scientific reasoning or clinical experience.

*Dosage.*—Ovarian substance may be given in powder or in tablets; corpus luteum may be given by the mouth in the form of the dried corpora lutea (also called lutein) either as a powder, in capsules, or in tablets, or subcutaneously in the form of a normal saline extract. Some clinicians direct its continuous use; others recommend that the administration be begun before the expected natural period and continued during it, and that the administration should be discontinued after the cessation of the period.

The preparations included in New and Nonofficial Remedies consist of dried ovarian substance and of the dried corpus luteum. It has been asserted that the corpus luteum of pregnancy is more efficient than that of menstruation.

**OVARIAN SUBSTANCE-ARMOUR.**—The entire fresh ovaries (including the corpora lutea) of the hog, cleaned,



dried and powdered, without the addition of either preservative or diluent.

*Actions and Uses.*—See Ovary.

*Dosage.*—From 0.06 to 0.2 Gm. (1 to 3 grains) three times daily.

Manufactured by Armour & Co., Chicago. No U. S. patent or trademark.

*Ovarian Substance Tablets-Armour.*—Each tablet contains ovarian substance 0.13 Gm. (2 grains).

*Dose.*—From 1 to 2 tablets three times a day.

Ovarian substance-Armour is a yellowish powder having a peculiar odor; it is partially soluble in water.

One part represents approximately  $6\frac{3}{4}$  parts of the fresh ovary of the hog. It contains gelatin, mucin, nuclein and the active constituent of the corpus luteum. On incineration, it should not yield more than 7 per cent. ash.

**DESICCATED CORPUS LUTEUM-ARMOUR.** — The fresh substance from the corpora lutea from cows' ovaries, removed, dried and powdered without the addition of preservatives or diluent.

*Actions and Uses.*—See Corpus Luteum.

*Dosage.*—From 0.13 to 0.65 Gm. (2 to 5 grains) twice daily.

Manufactured by Armour & Co., Chicago. No U. S. patent or trademark.

*Corpus Luteum Tablets.*—Each tablet contains desiccated corpus luteum-Armour, 2 grains.

*Corpus Luteum Capsules, 5 grains.*—Each capsule contains desiccated corpus luteum-Armour 5 grains.

*Corpus Luteum Capsules, 2 grains.*—Each capsule contains desiccated corpus luteum-Armour 2 grains.

Desiccated corpus luteum-Armour is a yellowish powder, having a peculiar odor; it is partly soluble in water.

One part represents approximately 5 parts of the fresh corpus luteum substance. It contains a true lipochrome which may be extracted by alcohol, ether or chloroform. On incineration, it should yield not more than 6 per cent. of ash.

**LUTEIN-H. W. & D.**—The fully developed corpora lutea of the hog freed from foreign material, dried and powdered. One part lutein-H. W. & D. represents approximately four parts of the fresh substance.

*Actions and Uses.*—See Corpus Luteum.

*Dosage.*—From 0.13 to 0.65 Gm. (2 to 10 grains), two or three times a day. Lutein-H. W. & D. is sold in the form of tablets only (see below).

Manufactured by Hynson, Westcott & Dunning, Baltimore, Md. No U. S. patent or trademark.

*Lutein Tablets-H. W. & D., 2 grains.*—Each tablet contains lutein. H. W. & D., 2 grains.

*Lutein Tablets-H. W. & D., 5 grains.*—Each tablet contains lutein. H. W. & D., 5 grains.

The fully developed, fresh corpora lutea of the hog are washed, freed from adhering foreign tissue, dried, powdered, and sufficient milk-sugar added so that 1 part should represent 4 parts of fresh substance.

### Parathyroid Gland

The administration of parathyroid has proved of value in a number of cases of tetany following the operative removal or injury of the parathyroid glands. It has prevented the attacks of tetany and seems undoubtedly, at times, to have prolonged life or to have saved it while the injured glands regained their functions. It has proved of value in some cases of gastric tetany and of infantile tetany, although in other cases the results were negative. It has been recommended in paralysis agitans, eclampsia and chorea (especially of adults), but the reports as to its usefulness in these conditions are very contradictory.

In some cases the use of the fresh glands or of the subcutaneous injection of extracts of the fresh glands has given better results than have the dried glands.

#### DESICCATED PARATHYROID GLAND-ARMOUR.—

The exterior parathyroids of the ox freed from fat, cleaned, dried and powdered, without the addition of preservative or diluent.

*Actions and Uses.*—See general article, Parathyroid Gland, above.

*Dosage.*—0.006 Gm. ( $\frac{1}{40}$  grain) four times a day.

Manufactured by Armour & Co., Chicago.

*Parathyroid Tablets-Armour.*—Each tablet contains desiccated parathyroid gland 0.003 Gm. ( $\frac{1}{20}$  grain).

A light yellow powder having a peculiar odor. Partly soluble in water.

One part represents approximately 6 parts of the fresh tissue. On incineration it should yield not more than 7 per cent. ash. It contains very small amounts of organically combined iodine.

### Pituitary Gland

The anterior lobe of this gland is essential to life; its total removal leads to death in a short time and its partial removal or disease to a condition of retarded growth or infantilism, to obesity and other disturbances of nutrition. The hyperactivity of the anterior lobe (as in acromegaly), leads to accelerated and abnormal growth—gigantism. These effects are believed to be due to an internal secretion.

*Physiologic Action.*—The posterior lobe (see also Pituitary Liquid) and *pars intermedia* contain a substance or substances having marked effects on plain muscle, especially that of the blood vessels and the uterus.

*Effect on the Circulation:* The intravenous or subcutaneous injection of preparations of the posterior lobe causes a distinct rise of blood pressure. This is largely due to a direct stimulating action on the blood vessel wall. The rise is smaller and less abrupt than that produced by epinephrin, but it is maintained longer. The heart is slowed probably because of the rise in pressure, and of a direct action on the cardiac muscle. There is often seen a sudden fall of pressure which is probably due to cardiac depression. A second injection may produce no effect or a fall in blood pressure. In practice, therefore, repeated injections must be given with great caution.

*Respiration:* There is probably no direct action on the respiratory center, but indirectly there appears to be some temporary depression which may be due to constriction of the bronchioles or to an effect on the pulmonary circulation.

*The Stomach and Intestine:* Peristalsis is markedly increased by direct action on the muscle coat of the intestinal tract. The substance, when given by the mouth, is not particularly reliable.

*On the Kidney:* Usually produces diuresis, which is sometimes followed by glycosuria. The cause of this diuresis is not completely worked out.

*The Lacteal Glands:* The amount of milk in lactating animals is increased temporarily, but this is probably due to an increased expulsion of milk from the lacteal glands. The drug does not increase the formation of milk.

*On the Uterus:* It causes a marked constriction of the uterus by a direct stimulating action on the muscle wall. This takes place in pregnant as well as nonpregnant animals.

*Therapeutic Uses.*—Extracts of the posterior lobe injected subcutaneously have been highly recommended in cases of uterine atony in postpartum and other forms of uterine hemorrhage. It should not be injected during the first stage of labor because if the os uteri is not fully open the energetic contractions may cause rupture of the uterus. It has also been recommended in shock and in various other conditions of low blood-pressure. It has been recommended in certain cases of pulmonary hemorrhage (though its use here, from our knowledge of its physiologic action, is not clear); it is also useful in intestinal paresis after abdominal operations. It is reported to have been used with success in cases of diabetes insipidus. Its repeated administration over long periods of time is not advisable. Its administration by the mouth seems to be less effective.

The preparations should be standardized physiologically, preferably by testing them on the uterus, using a definite amount of beta-iminazolyethylamine hydrochloride as a standard.

The administration of the anterior lobe has given favorable results in the later stages of acromegaly and in the condition known as *dystrophia adiposogenitalis*, in certain other cases of impotency; also in some cases of obesity. It is contra-indicated in the early stages of acromegaly.

**PITUITARY BODY DESICCATED-ARMOUR.**—The dried substance of the entire pituitary body of the ox, including the infundibulum and the anterior and posterior lobes without the addition of preservative or diluent. It is said to contain all the active principles naturally existing in the gland.

*Actions and Uses.*—See preceding general article, Pituitary Gland.

*Dosage.*—From 0.06 to 0.2 Gm. (1 to 3 grains) three times a day.

Manufactured by Armour & Co., Chicago. No U. S. patent or trademark.

*Pituitary Tablets-Armour.*—Each tablet contains desiccated pituitary body 0.06 Gm. (1 grain).

Pituitary body desiccated-Armour is a light yellowish-gray powder practically odorless and tasteless. One part represents approximately 4 parts of fresh gland.

**DESICCATED PITUITARY SUBSTANCE (ANTERIOR LOBE)-ARMOUR.**—The anterior lobe from the pituitary of the ox, separated, dried and powdered without the addition of preservative or diluent.

*Actions and Uses.*—See preceding general article, Pituitary Gland.

*Dosage.*—From 0.05 to 0.20 Gm. (1 to 4 grains) in powder or tablet.

Manufactured by Armour & Co., Chicago.

Desiccated pituitary substance (anterior lobe)-Armour is a light grayish-yellow powder with a slight peculiar odor; it is partly soluble in water.

One part represents approximately 4.5 parts of the fresh substance. On incineration it should yield not more than 6.5 per cent. ash.

**DESICCATED HYPOPHYSIS.**—For description see the U. S. Pharmacopeia under Hypophysis Sicca.

*Actions and Uses.*—See preceding general article, Pituitary Gland.



**DESICCATED PITUITARY SUBSTANCE (POSTERIOR LOBE)-ARMOUR.**—The posterior lobe from the pituitary of the ox, separated, dried and powdered without the addition of preservative or diluent.

*Actions and Uses.*—See preceding general article, Pituitary Gland.

*Dosage.*—From 0.5 to 0.20 Gm. (1 to 4 grains) in powder or tablet.

Manufactured by Armour & Co., Chicago.

Desiccated pituitary substance (posterior lobe)-Armour is a light grayish-yellow powder with a slight peculiar odor; it is partly soluble in water.

One part represents approximately 4.5 parts of the fresh substance. On incineration it should yield not more than 6.2 per cent. of ash.

**SOLUTION OF HYPOPHYSIS.**—For description see the U. S. Pharmacopeia under Liquor Hypophysis.

*Actions and Uses.*—See preceding general article, Pituitary Gland.

**Pituitary Liquid. — Extractum Hypophysis Cerebri Liquidum-Armour.**—A sterile solution containing the active principle of the posterior lobe of the pituitary body of cattle, free from preservatives. It is physiologically standardized according to the method of G. B. Roth, Bulletin No. 100, U. S. Hygienic Laboratory.

*Actions and Uses.*—See preceding general article, Pituitary Gland.

*Dosage.*—1 Cc. (15 minims) repeated in one hour if necessary. Pituitary liquid should be administered intramuscularly in the gluteal region under strict antisepsis in order to secure quick action and prevent necrosis. Pituitary liquid is supplied in 1 Cc. ampules only, bearing an expiration date.

Manufactured by Armour & Co., Chicago. No U. S. patent or trademark.

*Ampoules Pituitary Liquid.*—Each ampule contains pituitary liquid 1 Cc.

Pituitary liquid is made from the posterior lobe of the pituitary body of cattle by finely mincing the fresh glands and extracting with acidulated water. As the active principle is not destroyed by heat, the liquid is heated to boiling for the purpose of removing coagulable proteins and is then further purified by removing organic impurities such as peptones and other proteins. One cubic centimeter of the clear colorless liquid is measured into ampules and sterilized.

Pituitary liquid is a clear, colorless liquid having a faint but characteristic odor and slightly salty taste.

Pituitary liquid gives the biuret reaction. Alkaloidal precipitants such as phosphomolybdic acid, phosphotungstic acid, bromine water, etc., all give faint but distinct precipitates of the active principle.

Pituitary liquid is standardized so that a dilution of not more than 1:20,000 nor less than 1:10,000 is equal to a 1:20,000,000 dilution of betaminazolyethylamine hydrochloride when the isolated uterus of the virgin guinea-pig is used.

**Solution of Hypophysis-Squibb.**—Solution of Pituitary Body.—A sterilized solution of the water-soluble active principles of the posterior lobe of the pituitary body of cattle, free from chemical preservatives. It is physiologically standardized according to the method of G. B. Roth (Bulletin 100, U. S. Hygienic Laboratory).

*Action and Uses.*—See preceding general article, Pituitary Gland.

*Dosage.*—1 Cc. (16 minims), given hypodermically, repeated in from thirty to sixty minutes if necessary. The skin at the point of injection should be sterilized, preferably by painting with tincture of iodine.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

Posterior lobes of the pituitary gland of cattle are ground, extracted with slightly acidulated water, heated, then filtered through sterile gauze or paper and the extract standardized. The resulting extract is then adjusted so as to correspond with the standard. It is then retested for its physiologic activity, filled into ampules, subjected to a final control test, and preserved by heating without the addition of preservatives.

Solution hypophysis-Squibb is a clear, colorless liquid, having a faint, characteristic odor and taste.

It is standardized so that a dilution of not more than 1:20,000 and not less than 1:10,000 is equal to a 1:20,000,000 dilution of betaminazolyethylamine hydrochloride when the isolated uterus of the virgin guinea-pig is used.

**Solution Pituitary Extract.**—An aqueous sterile solution of a purified extract of the posterior (infundibular) lobe of the pituitary gland of the ox, preserved by addition of camphor water and 0.5 per cent. of boric acid. Each cubic centimeter is assayed to correspond in strength to 0.2 Gm. of the fresh posterior lobe.

*Actions and Uses.*—See preceding general article, Pituitary Gland.

*Dosage.*—The average adult dose is 1 Cc. Solution pituitary extract should be administered intramuscularly in the gluteal region under strict asepsis in order to secure quick action and prevent necrosis.

Manufactured by H. K. Mulford Co., Philadelphia. No U. S. patent or trademark.

*Ampuls Solution Pituitary Extract, 1 Cc.*—Each ampule contains solution pituitary extract 1 Cc.

*Ampuls Solution Pituitary Extract, 0.5 Cc.*—Each ampule contains solution pituitary extract 0.5 Cc.

Fresh posterior lobes of the pituitary gland of the ox are ground, dried, defatted, extracted with acidulated water, purified by heating to coagulate inactive protein matter, and the solution so obtained assayed by the isolated uterus method (*Jour. Am. Pharm. Assn.*, June, 1914, p. 808). After adjustment to proper strength it is sealed in ampules and sterilized by heat.

Solution pituitary extract is an almost colorless liquid having a faint odor of camphor.

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**OSMIUM TETROXIDE.**—*Osmium Tetroxidum.*—Osmic Acid.—Osmium Anhydride.— $\text{OsO}_4$ .—The anhydride of a theoretical acid obtained by the action of nitrohydrochloric acid on osmium.

*Actions and Uses.*—Intraneural injections are used to produce degeneration of nerves for the relief of persistent neuralgias. The treatment is best applied by injecting from 0.5 to 1 Cc. of a fresh 1 or 2 per cent. solution directly into the preferably exposed nerve. The result is sometimes immediate, but more commonly it is not complete until after one or two weeks, or it may even fail entirely. If successful, the effects may persist for several months, when it may become necessary to repeat the injection as the cure is rarely, if ever, permanent. The local reaction is always painful, but not serious. It is not advisable, perhaps, to use osmium tetroxide in renal disease.

Osmium tetroxide occurs in the form of white or yellowish crystals which are slowly soluble in water (1:50); it is also soluble in alcohol and ether but the solutions decompose. Osmium tetroxide melts at 40 C. and boils at about 100 C. It evaporates even at ordinary temperatures, yielding very irritating and extremely poisonous vapors, attacking the eyes and lungs. It is decomposed by contact with organic substances (*Brit. Codex*, 1907).

From aqueous acidified solutions of osmium tetroxide, hydrogen sulphide precipitates brown osmium sulphide,  $\text{OsS}_4$  which is insoluble in ammonium sulphide. An aqueous solution of osmium tetroxide decolorizes indigo solution. Iodine is liberated from potassium iodide solutions by osmium tetroxide. Treated with sulphurous acid, aqueous solutions of osmium tetroxide become yellow, turning to brown and finally becoming blue; tannic acid produces a red color, becoming brown; ferric chloride and alcohol reduce osmium tetroxide to the metal osmium.

**Osmic Acid-Merck.**—A nonproprietary brand complying with the standards for osmium tetroxide.

Merck & Co., New York, distributors.

## PARAFFIN FOR FILMS (SURGICAL PARAFFIN PLASTIC PARAFFIN)

Paraffin intended for application to burns, etc., should be solid at body temperature, but be more ductile and pliable than the official paraffin (Paraffinum, U. S. P.) and be liquid at or below 50 C. A thin film when prepared and tested as described below should be pliable at or below 28 C. and ductile at or below 31 C. At body temperature (38 C.) it should be pliable, and adhere to, but permit ready detachment from, the skin.

*Actions and Uses.*—Paraffin for films acts mechanically. When applied to burns and denuded surfaces, it provides an air-excluding dressing which relieves pain, forming a soft, pliable splintlike covering to wounded surfaces, keeps the parts at a relatively uniform temperature, immobilizes the epidermal tissue, and may aid in the formation of new tissue by acting as a scaffolding for newly formed cells.

Paraffin for films is used mainly in the treatment of burns. It is said to be useful in the treatment of "frostbite," "chilblains," and for covering denuded surfaces. It is also employed to prepare "paraffin-covered bandages" and to seal gauze dressings.

*Dosage.*—In the paraffin treatment of burns the wound, after preparatory treatment, is dried and a thin coating of either liquid petrolatum or melted paraffin for films (at a temperature of about 53 C.) is applied by means of an atomizer or brush. This is followed by the application of a thin layer of cotton and then another layer of the melted paraffin; the dressing is finished by covering with cotton and bandaging.

The melting point of paraffin for films is determined by the method of the U. S. Pharmacopoeia, IX, p. 596.

The pliability and ductility of paraffin is determined as follows: A little of the melted substance is poured on water having a temperature of about 40 C. so as to form a number of separate films. The temperature of the bath is then gradually lowered by the addition of cold water to determine the pliability and ductility. (Pliability test). The film while immersed in water is doubled on itself and the temperature of the water observed at which the film breaks sharply on *one* fold. (Ductility test.) The film is stretched while under water and the temperature of the water noted at which the film breaks sharply and evenly.

A small surface of the forearm is painted with melted paraffin, covered with a thin layer of cotton, another coat of paraffin painted on the cotton, and then dressed with cotton and bandage. After one hour, the film should remain attached to the skin, showing it adherent but easily removable.

**STANOLIND SURGICAL WAX**—A brand of paraffin for films, melting at 47 C., being pliable at or below 25 C. and ductile at or below 29 C.



*Actions, Uses and Dosage.*—See preceding general article, Paraffin for Films (Surgical Paraffin, Plastic Paraffin).

Manufactured by the Standard Oil Company of Indiana, Chicago.

**PARRESINE.**—A mixture composed of paraffin (melting point 48 to 49 C.), 94 to 96 per cent.; gum elemi, 0.20 to 0.25 per cent.; Japan wax 0.40 to 0.50 per cent.; asphalt, 0.20 to 0.25 per cent., and eucalyptol, 2 per cent. To this mixture is added 0.5 to 1.0 per cent. solution of alkannin in eucalyptol and a minute quantity of gentian violet, these being employed to bring the product to a standard color.

*Actions, Uses and Dosage.*—See preceding general article, Paraffin for Films (Surgical Paraffin, Plastic Paraffin).

Prepared by the Abbott Laboratories, Chicago. No U. S. patent. U. S. trademark applied for.

*Parresined Lace-Mesh Surgical Dressing.*—Net mesh gauze impregnated with and containing from 45 to 50 per cent. of parresine.

Parresine has the properties of paraffin, slightly modified by the addition of gum elemi, Japan wax and asphalt.

It is of a grayish smoky color, has the odor of eucalyptol, and melts at 47 to 48 C. (117 to 119 F.).

## PARSLEY-SEED PREPARATIONS

**APIOL.**—*Apiolum Crystallisatum.*—Parsley Camphor.— $\text{CH}_2:\text{CH}.\text{CH}_2.\text{C}_6\text{H}(\text{OCH}_3)_2:\text{O}:\text{CH}_2\text{CH}.$ —2,5-dimethoxy-3,4-methendioxy-1<sup>2</sup>propenylbenzene, derived from 2,3,4,5-tetrahydroxy-1-propen (1<sup>2</sup>) yl-benzene,  $\text{C}_6\text{H}(\text{OH})_4(\text{CH}_2\text{CH}:\text{CH}_2).$

*Actions and Uses.*—Apiol is said to produce cerebral excitation similar to that induced by coffee and in larger doses a species of intoxication, with vertigo, ringing in the ears and severe frontal headache.

Apiol has been used as an antiperiodic, but is regarded as of inferior rank for this purpose. It has also been recommended in the treatment of amenorrhea.

*Dosage.*—From 0.13 to 0.3 Gm. (2 to 5 grains) in capsules, as an emmenagogue; from 0.3 to 1 Gm. (5 to 15 grains) as an antipyretic.

Apiol may be obtained by extracting the oleoresin (oleoresin of parsley-seed) with ether and subsequent purification. It may also be obtained by submitting parsley-seed to steam distillation, cooling the volatile oil and collecting and purifying the crystals which separate.

Apiol crystallizes in long needles, having a faint odor of parsley, melting at 30 C. and boiling at 294 C. It is insoluble in water but readily soluble in alcohol and ether. With strong sulphuric acid it forms a blood-red solution. Apiol is not affected by aqueous solutions of potassium or sodium hydroxide, but by alcoholic solutions of potassium or sodium hydroxide it is gradually converted to isoapiol, which melts at 56 C.

**Apiol-Merck.**—A nonproprietary brand complying with the standards for apiol.

Merck & Co., New York, distributors.

## PERBORATE PREPARATIONS

Analogous to the metallic peroxides (discussed under "Peroxides") are the inorganic peracids. Of these, perboric acid has been introduced into medicine in the form of sodium perborate. This preparation is decomposed by water into hydrogen peroxide and sodium metaborate. It is used like the metallic peroxides.

**SODIUM PERBORATE.**—For description see the U. S. Pharmacopeia under Sodii Perboras.

**Sodium Perborate-Merck.**—A nonproprietary brand complying with the standards for sodium perborate.

Merck & Co., New York, distributors.

**Sodium Perborate-P. W. R.**—A nonproprietary brand complying with the standards for sodium perborate.

Manufactured by Powers-Weightman-Rosengarten Co., Philadelphia.

**Sodium Perborate-R. & H.**—A nonproprietary brand complying with the standards for sodium perborate.

Manufactured by the Roessler & Hasslacher Chemical Co., New York.

**PEROGEN BATH.** — Oxygen Bath Salts, Perogen.—A preparation consisting of a catalyzer and sodium perborate capable of yielding 10 per cent. of oxygen, the two substances being wrapped separately.

*Actions and Uses.*—The catalyzer is a medicinally indifferent substance. When the two substances are mixed with water the catalyzer causes the liberation of the available oxygen of the sodium perborate. The oxygen bath thus obtained is said usually to reduce the bloodpressure and pulse-rate to a much greater extent than the ordinary bath. It is claimed to have marked tranquilizing and somnifacient effects. It is said to be useful in cardiac affections with high vascular tension and excitement, neuroses, insomnia, chronic nephritis, and skin diseases in which hydrogen dioxide is indicated.

*Dosage.*—One bath daily until twenty-four or forty-eight have been taken, with occasional intermissions.

Manufactured by Morgenstern & Co., New York. U. S. patent No. 969,073 (Aug. 30, 1910; expires 1927). U. S. trademark No. 75,982.

The catalyzer is a light yellow odorless powder, and is made by a method which is the subject of a patent application now pending. The oxygen contents may be determined by any of the well known methods.

## PEROXIDES

The peroxides are compounds each of which contains within its molecule a complex of two oxygen atoms one of which is readily available for oxidizing purposes. The metallic peroxides may be considered as having been derived from hydrogen peroxide by replacement of its hydrogen by metallic radicals or kations, while the organic peroxides are similarly considered as having been derived by replacement of the hydrogen by carbon-containing groups (organic radicals).

Hydrogen peroxide is a combination of two atoms of hydrogen with two atoms of oxygen, one of the latter being given off to oxidizable substances, leaving a residue of water. In the presence of catalase, a ferment found in all cells, it is readily decomposed. The liberated oxygen sometimes causes considerable effervescence. For this reason it is dangerous to inject it into closed body cavities or into abscesses from which the gas has not a free exit. Hydrogen peroxide is official as liquor hydrogenii dioxi. This preparation is a germicide when diluted with not more than twice its volume of water. Diluted with an equal volume of water it destroys typhoid bacilli in two and one-half minutes.

### Metallic Peroxides

Metallic peroxides are compounds in which the hydrogen of hydrogen peroxide has been replaced by metals, and which are readily decomposed with liberation of hydrogen peroxide, or of oxygen. The peroxides of several metals have been suggested as substitutes for the hydrogen peroxide solution official as liquor hydrogenii dioxi.

*Actions and Uses.*—Like hydrogen peroxide, the metallic peroxides depend for their value on the readiness with which a part of their oxygen becomes active. They are claimed to possess advantages over solution of hydrogen peroxide, because the oxygen is set free more gradually. Among themselves the metallic peroxides differ in their action in accordance with their solubility and the alkalinity produced by interaction of the peroxide with water. The action of peroxides is also affected by the nature of the metal which goes into solution when the peroxide is decomposed. Thus, the use of sodium peroxide is limited by the strong base formed when it dissolves in water and that of zinc peroxide by the astringent action of zinc solutions.

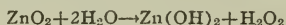
Because of the strong oxidizing effects on the lower organisms, the peroxides have been recommended as a convenient means of sterilizing water; thus a mixture has been used containing magnesium peroxide 0.2 Gm. and tartaric acid 0.5 Gm., the latter favoring the decomposition of the peroxide. It has been proposed to employ the oxidizing effect of peroxides in the treatment of skin diseases, by using a mixture of zinc peroxide, 10 parts; potassium iodide, 5 parts, and tar-

taric acid, 1 part, from which on contact with moisture iodine is gradually liberated. As ingredients of dentifrices magnesium and strontium peroxide have been used.

Internally the peroxides have been claimed to be of value as gastric and intestinal antiseptics and to be of use in the treatment of acid dyspepsia, abnormal fermentation and summer diarrhea of infants.

The commercial products are usually mixtures containing but a limited amount of real peroxide; for example, commercial "magnesium peroxide" contains but about 15 per cent. of magnesium peroxide while commercial "sodium peroxide" contains about 75 per cent. of sodium peroxide.

The different peroxides vary considerably in their stability, their solubility and in their ease of decomposition in solution. In solutions of acids the peroxides are decomposed, forming hydrogen peroxide and the salt of the metallic radical of the peroxide. In this way the entire active oxygen content of the peroxide is quickly made available in the form of hydrogen peroxide in solution. Water dissolves only minute quantities of these peroxides, but it decomposes them with varying degrees of readiness. Thus zinc peroxide, although very insoluble, is decomposed by water into zinc hydroxide and hydrogen peroxide as follows:



In general, the energy of the oxidizing powers of different peroxides varies in direct ratio to the alkalinity of the solution produced in their decomposition. The variation in the alkalinity solutions formed affects the therapeutic uses of the peroxide. Sodium peroxide is not desirable for therapeutic use because of the formation of the strongly alkaline solution of sodium hydroxide (caustic soda). Magnesium and zinc peroxide, on the other hand, yield weakly alkaline solutions and are for that reason more desirable. In these cases oxygen is evolved slowly, producing a continuous effect.

**CALCIUM PEROXIDE.**—*Calcium Peroxidatum.*—A mixture consisting essentially of calcium peroxide (the calcium salt,  $\text{CaO}_2$ , of hydrogen peroxide) and calcium hydroxide and carbonate, containing not less than 60 per cent. calcium peroxide, equivalent to 13.3 per cent. available oxygen.

*Actions and Uses.*—See Peroxides.

*Dosage.*—From 0.06 to 0.3 Gm. (1 to 5 grains) in water or with sodium bicarbonate, two to three times daily.

Calcium peroxide is a light, cream-colored, odorless and tasteless powder. It is practically insoluble in water, but by such contact it is gradually decomposed into hydrogen peroxide and calcium hydroxide, the hydrogen peroxide being further decomposed by the alkaline calcium hydroxide with liberation of oxygen. It is decomposed by dilute acids with formation of a solution containing hydrogen peroxide.

If a few milligrams of calcium peroxide be shaken with 10 Cc. water and 1 drop diluted sulphuric acid, and a few cubic centimeters of ether added, the subsequent addition of a drop of potassium dichromate solution will produce a blue color in the aqueous layer. On shaking, the blue color will pass into the ethereal layer. If 1 Gm. calcium



peroxide be dissolved in 25 Cc. dilute nitric acid and 2 Cc. tenth-normal silver nitrate added to the solution and the resulting precipitate filtered off, the further addition of a few drops of silver nitrate solution to the filtrate should produce no turbidity. If 1 Gm. calcium peroxide be exposed to the full heat of a Bunsen flame for five minutes, then dissolved in 25 Cc. dilute hydrochloric acid and the solution made up to 100 Cc., a solution will result which will conform to the following tests: Ten Cc. of the solution, to which ammonium hydroxide in excess has been added, should yield a white precipitate on the addition of ammonium oxalate solution. Ten Cc. of the solution saturated with hydrogen sulphide should yield no precipitate, nor become colored. Ten Cc. of the solution should yield not more than a turbidity on the addition of barium chloride solution. Ten Cc. of the solution, after addition of a slight excess of ammonium hydroxide and acidification with acetic acid, should yield no turbidity on the addition of potassium dichromate solution. If 0.2 to 0.3 Gm. calcium peroxide, weighed into a flask, be shaken with 25 Cc. water, then 25 Cc. dilute hydrochloric acid added, the titration of this solution with tenth-normal potassium permanganate should indicate the presence of not less than 60 per cent. calcium peroxide. (One Cc. tenth-normal potassium permanganate is equivalent to 0.0036 Gm.,  $\text{CaO}_2$ ).

**Calcium Peroxide-Merck.**—A nonproprietary brand complying with the standards for calcium peroxide.

Merck & Co., New York, distributors.

**Calcium Peroxide-P. W. R.**—A nonproprietary brand complying with the standards for calcium peroxide.

Manufactured by Powers-Weightman-Rosengarten Co., Philadelphia.

**Calcium Peroxide-R. & H.**—A nonproprietary brand complying with the standards for calcium peroxide.

Manufactured by the Roessler & Hasslacher Chemical Co., New York.

**MAGNESIUM PEROXIDE.**—**Magnesium Peroxidatum.**—**Magnesium Superoxide.**—**Magnesium Dioxide.**—A mixture consisting essentially of magnesium peroxide (the magnesium salt,  $\text{MgO}_2$ , of hydrogen peroxide) and magnesium oxide with water of hydration, containing not less than 15 per cent. of magnesium peroxide, equivalent to 4.3 per cent. of available oxygen.

*Actions and Uses.*—Magnesium peroxide, because of its property of yielding oxygen, is said to be of value as a gastric and intestinal antiseptic. It has been recommended in chlorosis, anemia, gout and rheumatism. It is also used as a constituent of dentifrices.

*Dosage.*—From 0.25 to 0.50 Gm. (4 to 7 grains) two or three times daily.

Magnesium peroxide is a white powder. It is practically insoluble in water, but by such contact is gradually decomposed into hydrogen

peroxide and magnesium hydroxide, the hydrogen peroxide being further decomposed by the alkaline magnesium hydroxide, with liberation of oxygen. It is decomposed by dilute acids with formation of a solution containing hydrogen peroxide.

If a few milligrams of magnesium peroxide be shaken with 10 Cc. water and 1 drop of dilute sulphuric acid, and a few cubic centimeters of ether added, the subsequent addition of a drop of potassium dichromate solution will produce a blue color in the aqueous layer; on shaking the blue color will pass into the ethereal layer. If 0.2 Gm. magnesium peroxide be boiled with 10 Cc. water, then cooled and filtered, the filtrate should be but faintly alkaline; and 5 Cc. of this filtrate on evaporation should leave only a trace of residue. If 1 Gm. magnesium peroxide be dissolved in 25 Cc. dilute nitric acid and 2 Cc. tenth-normal silver nitrate added to the solution and the resulting precipitate filtered off, the further addition of a few drops of silver nitrate solution to the filtrate should not produce a turbidity. If 1 Gm. magnesium peroxide be exposed to the full heat of a Bunsen flame for five minutes, then dissolved in 25 Cc. dilute hydrochloric acid and the solution made up to 100 Cc., a solution will result which will conform to the following tests: Ten Cc. of this solution, after adding ammonium chloride solution and ammonium hydroxide solution in excess, a few drops of ammonium oxalate solution and heating, the precipitate, if any be formed, filtered out and the filtrate treated with sodium phosphate solution, will yield a white precipitate. Ten Cc. of the solution saturated with hydrogen sulphide should yield no precipitate and should not become colored. Ten Cc. of the solution, to which 10 Cc. ammonium chloride solution and ammonium hydroxide in excess have been added, should yield not more than a turbidity on the addition of ammonium carbonate. Ten Cc. of the solution made alkaline with ammonium hydroxide solution, and then made slightly acid with acetic acid, should yield no turbidity on the addition of potassium dichromate solution. If 0.2 to 0.3 Gm. magnesium peroxide, weighed into a flask, be dissolved with 20 Cc. dilute sulphuric acid, the solution diluted with 50 Cc. water, the titration of this solution with tenth-normal potassium permanganate should indicate the presence of not less than 15 per cent. magnesium peroxide,  $MgO_2$ . (One Cc. of tenth-normal permanganate is equivalent to 0.0028 Gm.  $MgO_2$ .)

**Magnesium Peroxide-P. W. R.**—A nonproprietary brand complying with the standards for magnesium peroxide.

Manufactured by Powers-Weightman-Rosengarten Co., Philadelphia.

**Magnesium Peroxide-R. & H.**—A nonproprietary brand complying with the standards for magnesium.

Manufactured by the Roessler & Hasslacher Chemical Co., New York.

**SODIUM PEROXIDE.**—*Sodii Peroxidum.*—*Bioxydum Natri.*—The sodium salt of hydrogen peroxide containing at least 90 per cent of sodium peroxid,  $Na_2O_2$ , equivalent to 18.4 per cent. available oxygen.

*Actions and Uses.*—Sodium peroxide is not used internally but has been used in acne, applied in the form of a paste prepared with liquid paraffin, or as a soap to remove comedones.

It has been suggested as an air purifier, this suggestion being based on the theory that the moisture of the air would liberate oxygen and the alkali simultaneously formed would absorb carbon dioxide.

Sodium peroxide occurs in the form of a white, or yellowish, amorphous powder. It is soluble in water, with evolution of heat, and forms a solution of hydrogen peroxide, from which latter oxygen is liberated by the heat of the reaction. It dissolves in cold dilute acids forming a solution of hydrogen peroxide. When heated sodium peroxide becomes darker, but on cooling resumes its original color. It does not react with alcohol, but it ignites ether on contact. A mixture with red phosphorus explodes under pressure or on being struck. It is an extremely powerful oxidizing agent.

Sodium peroxide should not respond to tests for sulphates, chlorides, phosphates, nitrates and heavy metals. If 1 Gm. or 1.5 Gm. sodium peroxide be weighed and gradually added with constant stirring to 950 Cc. of dilute sulphuric acid (1 per cent.) and the solution made up to 1,000 Cc., the titration of 100 Cc. of this solution with tenth-normal potassium permanganate should indicate the presence of not less than 90 per cent. sodium peroxide. Each cubic centimeter of tenth-normal permanganate used corresponds to 0.0039 Gm. sodium peroxide ( $\text{Na}_2\text{O}_2$ ).

**Sodium Peroxide-P. W. R.**—A nonproprietary brand complying with the standards for sodium peroxide.

Manufactured by Powers-Weightman-Rosengarten Co., Philadelphia.

**Sodium Peroxide-Merck.**—A nonproprietary brand complying with the standards for sodium peroxide.

Merck & Co., New York, distributors.

**Sodium Peroxide-R. & H.**—A nonproprietary brand complying with the standards for sodium peroxide.

Manufactured by the Roessler & Hasslacher Chemical Co., New York.

**Oxone.**—Oxone is a proprietary name applied to fused sodium peroxide containing a fractional percentage of a catalytic agent. It is said to yield its entire content of available oxygen in gaseous form, on contact with water.

Manufactured by the Roessler & Hasslacher Chemical Co., New York. U. S. patent Nos. 788,256 (April 25, 1905; expires 1922) and 884,563 (April 14, 1908; expires 1925). U. S. trademark No. 46,673.

**STRONTIUM PEROXIDE.**—Strontium Peroxidatum.—A mixture consisting essentially of strontium peroxide (the strontium salt,  $\text{SrO}_2$ , of hydrogen peroxide), and strontium hydroxide containing at least 84 per cent. strontium peroxide, equivalent to 11.2 per cent. available oxygen.

*Actions and Uses.*—See preceding general article, Peroxides.

*Dosage.*—Strontium peroxide is used in the form of ointments and as a dusting powder.

Strontium peroxide is a fine, white, odorless and tasteless powder. It is practically insoluble in water, but by such contact is gradually decomposed into hydrogen peroxide and strontium hydroxide, the hydrogen peroxide being further decomposed by the alkaline strontium hydroxide with liberation of oxygen. It is decomposed by dilute acids with formation of a solution containing hydrogen peroxide. If a few milligrams of strontium peroxide be shaken with 10 Cc. water and 1 drop dilute sulphuric acid and a few cubic centimeters of ether added, the subsequent addition of a drop of potassium dichromate will produce a blue color in the aqueous layer. On shaking, the blue color will pass into the ethereal layer. If 1 Gm. strontium peroxide be dissolved in 25 Cc. dilute nitric acid and 2 Cc. tenth-normal silver nitrate added to the solution and the resulting precipitate filtered off, the further addition of a few drops of silver nitrate solution to the filtrate should not produce more than a turbidity. If 1 Gm. strontium peroxide be exposed to the full heat of a Bunsen flame for five minutes, then dissolved in 25 Cc. dilute hydrochloric acid and the solution made up to 100 Cc., a solution will result which will conform to the following tests: Ten Cc. of the solution made alkaline by the addition of ammonium hydroxide and then slightly acid with acetic acid should yield a white precipitate on the addition of ammonium sulphate solution. Ten Cc. of the solution saturated with hydrogen sulphide should yield no precipitate and should not become colored. Ten Cc. of the solution should yield not more than a turbidity on the addition of barium chloride solution. Ten Cc. of the solution which has been made alkaline with ammonium hydroxide and then acidified with acetic acid should yield no turbidity on the addition of potassium dichromate solution. If 0.2 to 0.3 Gm. strontium peroxide, weighed into a flask, be treated with 50 Cc. water and dissolved by addition of 20 Cc. dilute hydrochloric acid, the titration of this solution with tenth-normal potassium permanganate should indicate the presence of not less than 84.5 per cent. strontium peroxide. (One Cc. tenth-normal potassium permanganate is equivalent to 0.0058 Gm.  $\text{SrO}_2$ )

**Strontium Peroxide-P. W. R.**—A nonproprietary brand complying with the standards for strontium.

Manufactured by Powers-Weightman-Rosengarten Co., Philadelphia.

**Strontium Peroxide-R. & H.**—A nonproprietary brand complying with the standards for strontium.

Manufactured by the Roessler & Hasslacher Chemical Co., New York.

**ZINC PEROXIDE.**—*Zincum Peroxidatum.*—A mixture consisting essentially of zinc peroxide (the zinc salt,  $\text{ZnO}_2$ , of hydrogen peroxide) and zinc oxide, containing at least 45 per cent. zinc peroxide, equivalent to 7.4 per cent. available oxygen.

*Actions and Uses.*—See general article, Metallic Peroxides.

*Dosage.*—Zinc peroxide may be used as a dusting powder either alone or mixed with tannin, or in the form of gauze, or in a 10 per cent. ointment.



Zinc peroxide is a yellowish white, voluminous, tasteless and odorless powder. It is practically insoluble in water, but by such contact is gradually decomposed into hydrogen peroxide and zinc hydroxide, the hydrogen peroxide being further decomposed by the alkaline zinc hydroxide with liberation of oxygen. It is decomposed by dilute acids with formation of a solution containing hydrogen peroxide. It is stable at 150 C. and thus may be sterilized.

If a few milligrams of zinc peroxide be shaken with 10 Cc. water and 1 drop of dilute sulphuric acid, a few cubic centimeters of ether added, the subsequent addition of a drop of potassium dichromate solution will produce a blue color in the aqueous layer; on shaking, the blue color will pass into the ethereal layer. If 1 Gm. zinc peroxide be dissolved in 25 Cc. dilute nitric acid and 2 Cc. tenth-normal silver nitrate added to the solution and the resulting precipitate filtered off, the further addition of a few drops of silver nitrate solution to the filtrate should not produce a turbidity. If 1 Gm. zinc peroxide be exposed to the full heat of a Bunsen flame for five minutes, then dissolved in 25 Cc. dilute hydrochloric acid and the solution made up to 100 Cc., a solution will result which will conform to the following tests: Ten Cc. of the solution made alkaline with ammonium hydroxide and then slightly acid with acetic acid should not become turbid on the addition of potassium dichromate solution. Ten Cc. of the solution saturated with hydrogen sulphide should yield no precipitate and should not become colored. Ten Cc. of the solution, to which 10 Cc. ammonium chloride solution and ammonium hydroxide in excess have been added, should yield not more than a turbidity on the addition of ammonium oxalate. Ten Cc. of the solution should yield a white flocculent precipitate on the addition of a few drops of potassium ferrocyanide solution. Ten Cc. of the solution should yield not more than a turbidity on the addition of barium chloride solution. If 0.2 to 0.3 Gm. zinc peroxide, weighed into a flask, be dissolved with 20 Cc. diluted sulphuric acid, the solution diluted with 50 Cc. water, the titration of this solution with tenth-normal potassium permanganate should indicate the presence of not less than 45 per cent. zinc peroxide. (One Cc. tenth-normal potassium permanganate is equivalent to 0.0048 Gm.  $\text{ZnO}_2$ .)

**Zinc Peroxide-Merck.**—A nonproprietary brand complying with the standards for zinc peroxide.

Merck & Co., New York, distributors.

**Zinc Peroxide-P. W. R.**—A nonproprietary brand complying with the standards for zinc peroxide.

Manufactured by Powers-Weightman-Rosengarten Co., Philadelphia.

**Zinc Peroxide-R. & H.**—A nonproprietary brand complying with the standards for zinc peroxide.

Manufactured by the Roessler & Hasslacher Chemical Co., New York.

**Peroxide Zinc Soap.**—*Sapo cum Zinci Peroxido.*—A proprietary preparation containing 10 per cent. zinc peroxide in the form of a soap. It is said to be useful as a vehicle for employing zinc peroxide in the treatment of skin diseases. Prepared by the Roessler & Hasslacher Chemical Co., New York. U. S. patent No. 787,776 (April 18, 1905; expires 1922). No U. S. trademark.

### Organic Peroxides

The organic peroxides are combinations of organic radicals with oxygen which is yielded to oxidizable substances. The principal organic peroxides are compounds of organic radicals with oxygen and on hydrolysis yield compounds known as the peracids. Thus acetyl-benzoyl peroxide is a combination of acetyl and benzoyl with oxygen. On hydrolysis it yields benzo-peracid and aceto-peracid, which exert marked oxidizing and germicidal action. Organic peroxides have been used locally as antiseptics and also have been administered internally with the hope that they will act as intestinal antiseptics.

**ACETOZONE.**—A mixture of equal parts of acetyl-benzoyl peroxide and an inert absorbent powder.

Acetyl-benzoyl peroxide,  $C_6H_5CO.O.O.COCH_3$ , corresponds to hydrogen peroxide,  $H_2O_2$ , in which the two hydrogen atoms have been replaced by the radicals of acetic acid (the acetyl group) and of benzoic acid (the benzoyl group).

**Actions and Uses.**—Acetyl-benzoyl peroxide belongs to a class of compounds known as the organic peroxides in which oxygen has been combined in such a way that it is somewhat slowly given off in a nascent condition. On contact with water it hydrolyzes, forming benzo-peracid and aceto-peracid, which exert marked oxidizing and germicidal action. In consequence of this change, these compounds are thought to be particularly adapted for internal administration.

It is said to be useful as an antiseptic in ophthalmic, aural and nasal practice, and to give good results by acting as an intestinal antiseptic when given internally, especially in typhoid fever.

**Dosage.**—Acetozone is generally employed in aqueous solution prepared as follows: Add acetozone to warm water in the proportion of 1 Gm. to 1,000 Cc. (15 grains to the quart), shake vigorously for five minutes, and allow to stand for about two hours. Decant the liquor as required. This solution may be drunk *ad libitum*, 2 quarts or more being taken by an adult in twenty-four hours. Acetozone is also used in oil solution as an inhalant.

Manufactured by Parke, Davis & Co., Detroit. U. S. patent No. 710,005 (Sept. 30, 1902; expires 1919) and No. 717,016 (Dec. 30, 1902; expires 1919). U. S. trademark.

**Acetozone Inhalant.**—Each 100 Gm. contains acetozone 1.0 Gm. (15 grains); chloretone (chlorbutanol), 0.5 Gm. (8 grains); refined liquid petroleum, 98.5 Gm.

Acetyl-benzoyl peroxide occurs in white, lustrous crystals, melting at 36.6 C. When heated it slowly decomposes and volatilizes. Water at 25 C. dissolves 1 part in 1,560 or 0.639 Gm. in 1,000 Cc. It is soluble in oils to the extent of about 3 per cent., slightly soluble in alcohol, and fairly so in ether, chloroform and carbon tetrachloride, though all

solvents slowly decompose it with the exception of neutral petroleum oils. In the presence of water it undergoes hydrolysis and slowly decomposes. This change, however, does not take place with sufficient rapidity to prevent its use in aqueous solution; in fact, such hydrolysis is necessary to develop its full germicidal activity. On account of its ready decomposition, acetozone should be kept in a dry place. For various reasons it has been found necessary to add an inert absorbent powder. As found in the market, acetozone is of a grayish white color, possessing the properties of the crystalline substance, with the exception that the absorbent powder employed is insoluble.

## PHENETIDIN DERIVATIVES

The phenetidins (derivatives of para-amino-phenol  $C_6H_4(NH_2)(OH)$ , 1:3) comprise chemical relatives of aniline (amino-benzene). The members of this group have similar properties and are more or less active according as they undergo decomposition in the system so as to yield either para-amino-phenol or acetyl-amino-phenol. They have a more or less pronounced action on the blood by which they produce hemolysis and destruction of the red blood corpuscles. They also act as heart depressants.

Acetphenetidin and its congeners are antipyretics and analgesics. They are extensively employed for the relief of pain, but for this purpose they should be used with caution in consideration of their poisonous properties.

They have also been considerably employed for the reduction of temperature in fever. Every newly discovered product related to acetphenetidin has been heralded as a "safe" antipyretic and free from poisonous effects on the blood and heart. Invariably, extended clinical experience has shown that all these preparations are to a greater or less degree hemolytic and depressing to the circulation. Hence their employment in the infectious fevers should be most cautious.

**ACETPHENETIDIN.**—For description see the U. S. Pharmacopeia under Acetphenetidinum.

*Actions and Uses.*—See Useful Drugs.

**Phenacetin.**—A nonproprietary name applied to Acetphenetidin, U. S. P. For description see the Pharmacopeia. The tests of identity and purity prescribed by the United States Pharmacopeia should apply to the product dispensed under this title.

**Holocaine Hydrochloride.**—See Anesthetics, Local.

**PHENOCOLL SALICYLATE.**—See Phenocoll Compounds.

**SALOPHEN.**—Acetylparaminophenyl Salicylate.—Acetpar-aminosalol.—1,4-Acetamino-Phenyl Salicylate.— $C_6H_4.OH.CO.O.C_6H_4.(NHCH_3CO)$ . The salicylic acid ester of 1,4-acetaminophenol,  $C_6H_4.(NHCH_3CO)(OH)$ .

*Actions and Uses.*—The actions of salophen resemble those of phenyl salicylate (salol). It is not changed in the stomach, but is broken up in the intestine, liberating salicylic acid and acetylparaminophenol, which, unlike phenol, is not toxic. It acts as an antirheumatic, antipyretic, antiseptic and analgesic. It is said to be useful in rheumatism, gout, typhoid fever, and as an intestinal antiseptic, in diarrhea and dysentery. Externally it has been applied in psoriasis and other itching skin diseases.

*Dosage.*—From 0.3 to 1 Gm. (5 to 15 grains), in powder, wafers or capsules. Externally in 10 per cent. ointment.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent expired.

Salophen is made by preparing paranitrophenol salicylate by a process similar to that of preparing phenyl salicylate (salol); converting this by means of reducing agents into pharaminophenol salicylate, and this into acetylparaminophenol salicylate by the action of acetic acid. This crude salophen so obtained is then purified by crystallization from benzene or alcohol.

It forms small, white, crystalline leaflets or powder, odorless and tasteless, melting at from 187 to 188 C., and containing 51 per cent. of salicylic acid. It is almost insoluble in cold water, more soluble in warm water, but freely soluble in watery solutions of the alkalies and in alcohol, ether and benzene, but not in petroleum benzin.

If its alkaline solution be boiled it gradually becomes blue; on continuing the boiling the color is discharged, but is again produced on cooling and exposure to air. On addition of ferric chloride to the alkaline solution the violet color characteristic of salicylic acid is produced, but a simple aqueous solution of salophen does not react with ferric chloride and should not be changed by silver nitrate. It forms a colorless solution with concentrated sulphuric acid.

It is incompatible with alkalies, which decompose it.

## PHENOCOLL COMPOUNDS

**PHENOCOLL SALICYLATE.**— $C_6H_4.OC_2H_5.NH.(CH_2NH_2.CO).C_6H_4.OH.COOH$ .—The salicylate of the synthetic base phenocoll.

*Actions and Uses.*—Phenocoll salicylate combines the therapeutic action of phenocoll (antipyretic, analgesic, see phenocoll hydrochloride) with those of salicylic acid (antiseptic, antirheumatic).

It is said to be useful in rheumatism, gout, chorea, pleuritis and fevers, especially in influenza, but is more toxic than the salicylates alone.



*Dosage.*—From 1 to 2 Gm. (15 to 30 grains).

Phenocoll salicylate is prepared by neutralizing a hot aqueous solution of salicylic acid with phenocoll and cooling the solution.

It forms fine, white, crystalline needles, having a sweetish taste, sparingly soluble in cold water (1:200), readily soluble in hot water. It gives a violet reaction with ferric chloride.

It is incompatible with soluble hydroxides and carbonates and with bodies which are incompatible with the salicylates in general.

**PHENOLPHTHALEIN.**—For description see the U. S. Pharmacopeia under Phenolphthaleinum.

*Actions, Uses and Dosage.*—See Useful Drugs.

**Phenolphthalein-Merck.**—A nonproprietary brand complying with the standards for phenolphthalein.

Merck & Co., New York, distributors.

**Phenolphthalein-Monsanto.**—A nonproprietary brand complying with the standards for phenolphthalein.

Manufactured by the Monsanto Chemical Works, St. Louis.

## PHENOLSULPHONATES

**CALCIUM PHENOLSUPHONATE.**—Calcii Phenolsulphonas.—Calcium Sulphocarbolate.— $[\text{C}_6\text{H}_4(\text{OH})\text{SO}_3]_2\text{Ca}$ . The neutral calcium salt of parphenolsulphonic acid.

*Actions and Uses.*—Calcium phenolsulphonate has the actions and uses of other phenolsulphonates (sulphocarbolates). It is believed by some to be an intestinal antiseptic, but most pharmacologists regard the antiseptic powers of the phenolsulphonates as feeble.

It may be prescribed in diarrhea and in diseased conditions in which it is believed that there is an undue amount of intestinal putrefaction.

*Dosage.*—The average dose is 0.5 Gm. (8 grains).

Calcium phenolsulphonate occurs as a white, or faintly pinkish-white, almost odorless powder, having an astringent, bitter taste. At high temperatures the salt chars, emits inflammable vapors having an odor of phenol, and finally leaves a residue of calcium sulphate. The salt is easily soluble in water and in alcohol.

An aqueous solution of the salt (1:100) should assume a pale violet color on the addition of ferric chloride test solution. An aqueous solution of the salt (1:100) should not respond to the time-limit test for *heavy metals* prescribed by the United States Pharmacopeia. An aqueous solution of the salt (1:100) acidified with a few drops of diluted hydrochloric acid should give no immediate turbidity after addition of 1 Cc. of barium chloride test solution (limit of *sulphate*). If dried to constant weight at 100 C. the salt should not lose more than 2 per cent. of its weight (absence of an undue amount of *water*). If from 0.5 to 1 Gm. of the salt be dried to constant weight at 100 C. and the dried substance be slowly ignited in an uncovered crucible (care being taken that the contents be freely exposed to the air) until

the weight becomes constant, the residue should amount to not less than 35.0 per cent. nor more than 36.0 per cent. of the weight of the dried substance.

**Calcium Phenolsulphonate-Abbott.**—A nonproprietary brand complying with the standards for calcium phenolsulphonate.

Manufactured by the Abbott Laboratories, Chicago.

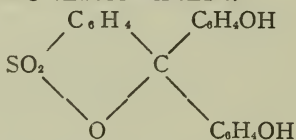
**Calcium Phenolsulphonate-M. C. W.**—A nonproprietary brand complying with the standards for calcium phenolsulphonate.

Manufactured by the Mallinckrodt Chemical Works, St. Louis.

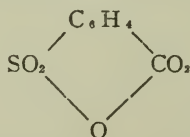
**Calcium Phenolsulphonate-P. W. R.**—A nonproprietary brand complying with the standards for calcium phenolsulphonate.

Manufactured by Powers-Weightman-Rosengarten Co., Philadelphia.

#### PHENOLSULPHONEPHTHALEIN.—



A product of the interaction of phenol and sulphobenzoic acid anhydride.



differing from phenolphthalein in that a CO group of the latter is replaced by a SO<sub>2</sub> group.

**Actions and Uses.**—Solutions of phenolsulphonephthalein injected into the tissues are readily absorbed, and are excreted mainly in the urine. A very small amount is excreted by the feces.

Phenolsulphonephthalein is used for determining the functional activity of the kidney. When injected intramuscularly or intravenously it begins to be excreted in normal cases in from five to ten minutes. In case of a deficient functional activity, the first appearance of its secretion is delayed. In normal cases, after intramuscular injections, almost the total amount is excreted within two hours (from 60 to 80 per cent.). Failure to excrete nearly the full amount within two hours indicates a deficient functional activity, and the degree

of this functional deficiency may be estimated by the proportionate amount excreted within two hours. The average normal eliminations after intravenous administration are 35 to 45 per cent. in fifteen minutes, 50 to 65 per cent. in thirty minutes and 65 to 80 per cent. in the first hour. (See *Jour. Pharm. and Exper. Therap.*, 1: 579, 1910; J. A. M. A., Sept. 2, 1911, p. 811, *Arch. Int. Med.*, March, 1912, p. 284.)

*Dosage.*—(See references above.) One Cc. of a sterile solution, containing 0.006 Gm. phenolsulphonephthalein as the monosodium salt, is injected into the lumbar muscles. Great care must be taken that all of the solution is injected.

From twenty minutes to half an hour before administering the test, the patient is given from 200 to 400 Cc. of water in order to insure free urinary secretion; otherwise delayed time of appearance may be due to lack of secretion.

Under aseptic precautions a catheter is introduced and the bladder completely emptied or the patient is allowed voluntarily to do so. Noting the time, 1 Cc. of a carefully prepared solution of the phenolsulphonephthalein containing 6 mg. to the cubic centimeter is accurately administered intramuscularly or intravenously by means of an accurately graduated syringe.

The urine is allowed to drain into a test tube in which has been placed a drop of 25 per cent. sodium hydroxide solution and the time of the appearance of the first faint pinkish tinge is noted.

In patients without urinary obstruction the catheter is withdrawn at the time of the appearance of the drug in the urine. If injected *intramuscularly* the patient is instructed to void into a receptacle at the end of one hour and ten minutes, and into a second receptacle at the end of the second hour. If injected *intravenously* the patient is instructed to void into a receptacle at the end of fifteen or thirty minutes or one hour.

When the passing of a catheter is disagreeable and no urinary retention is present, its use can be dispensed with and the time of appearance of the drug disregarded.

The urine collected is made alkaline with a 25 per cent. solution of sodium hydroxide and then diluted to 1 liter. The solution is thoroughly mixed and a small filtered portion taken to compare with the standard which is used for all of these estimations. Comparison is made in a colorimeter, a special form of which has been devised for this purpose.

Phenolsulphonephthalein is a bright-red crystalline powder, slightly soluble in water and in alcohol with formation of a yellow solution; it is insoluble in ether. It is soluble in dilute alkalis with formation of a solution whose color is a purer red than alkaline phenolphthalein, while a strongly alkaline solution is purple. In solution it is sensitive to carbonic acid just as phenolphthalein is. It is readily soluble in sodium carbonate solution and shows stronger acid properties than any of the related phthaleins. The substance at first has a slightly sweetish taste, which changes to a disagreeable bitter taste.

**Phenolsulphonephthalein-H. W. & D.**—Phenolsulphonephthalein made by a special process and said to be exceptionally pure. Phenolsulphonephthalein-H. W. & D., is sold in the form of ampules only (see below).

Manufactured by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

*Phenolsulphonephthalein Ampules-H. W. & D.*—One Cc. of solution contains 6 mg. phenolsulphonephthalein, in the form of the monosodium salt. Each ampule contains more than 1 Cc.

## PHENYLCINCHONINIC ACID AND PHENYL-CINCHONINIC ACID DERIVATIVES

Phenylcinchoninic acid, which was introduced into therapeutics under the name "atophan," and its compounds, are derived from quinolin carboxylic acid. Phenylcinchoninic acid is phenyl-quinolin-carboxylic acid. Novatophan is ethyl-methyl-phenyl-quinolin-carboxylic acid or the ethyl ester of paratophan. Phenylcinchoninic acid has a slightly bitter taste, while novatophan is practically tasteless; otherwise, their actions are identical.

*Actions and Uses.*—Phenylcinchoninic acid and its derivatives stimulate the kidneys so as to increase the amount of urine and have a selective action on the excretion of uric acid, which is increased in greater ratio than the increase in amount of urine. Under a purin-free diet the amount of uric acid in the blood is reduced one-half; when exogenous purins are given, the total amount is rapidly excreted so that the content of uric acid in the blood remains at normal or below. Its influence on uric acid excretion is stronger and is exerted more promptly than that of sodium salicylate. The action of phenylcinchoninic acid grows weaker after the first three hours and is practically terminated in nine hours after the administration of the dose. The amount of ammonia and of total nitrogen in the urine are slightly increased during the action of phenylcinchoninic acid, but not in proportion to the increase in the uric acid of the urine. Phenylcinchoninic acid does not increase the leukocytes, the purin bases or the phosphoric acid. There is no evidence of increased formation of uric acid or of any effect on deposited urates. It is stated, however, that the tophi in gout grow smaller under the use of phenylcinchoninic acid.

Phenylcinchoninic acid is useful in acute gout; it relieves pain in this disease, acting more promptly than colchicum and without undesirable by-effects. In nonuratic joint affections, particularly acute articular rheumatism, favorable results are reported, while the chronic forms seem to yield to phenylcinchoninic acid only in isolated cases. It is said that it relieves the pain of sciatica, but in a case reported by



## PHENYLCINCHONINIC ACID DERIVATIVES 227

McLester (*Arch. Int. Med.*, December, 1913, p. 739) it failed to relieve the pain, although the amount of uric acid in the blood was markedly reduced.

**Dosage.**—In gout the dose of phenylcinchoninic acid is from 0.5 Gm. (8 grains) four times a day to 1 Gm. (15 grains) three times a day suspended in large quantities of water. In order to prevent the precipitation of free uric acid from the urine with possibly resulting renal colic, Weintraub considers it necessary to administer simultaneously 15 Gm. (225 grains) of sodium bicarbonate in the course of the first day and from 5 to 10 Gm. (75 to 150 grains) on the following days. In articular rheumatism Heller prescribes daily doses of from 3 to 5 Gm. (45 to 75 grains).

2-phenyl-quinolin-4-carboxylic acid was described by Doebner and Giesecke in 1887 (*Ann. d. Chem.* [Liebig's], cxlii, 291), who prepared it by warming together pyroracemic acid, benzaldehyde and anilin in alcoholic solution. Its therapeutic action was described by Nicolai<sup>r</sup> and Dohrn in 1908 (*Deutsch. Arch. f. klin. Med.*, 93: 331).

**PHENYLCINCHONINIC ACID.**—For description see the U. S. Pharmacopeia under *Acidum Phenylcinchoninicum*.

**Actions, Uses and Dosage.**—See general article, Phenylcinchoninic Acid and Phenylcinchoninic Acid Derivatives.

**Atophan.**—A proprietary name applied to phenylcinchoninic acid. It complies with the standards for phenylcinchoninic acid, U. S. P.

Manufactured by Schering & Glatz, Inc., New York. U. S. patent No. 1,075,171 (Oct. 7, 1913; expires 1930). U. S. trademark No. 84,596.

**Atophan Tablets.**—Each tablet contains atophan 0.5 Gm. (7½ grains) and a small amount of cacao.

**Phenylcinchoninic Acid-Abbott.**—A brand of phenylcinchoninic acid, U. S. P.

Manufactured by the Abbott Laboratories, Chicago, under U. S. patent No. 1,075,171 (Oct. 7, 1914; expires 1930) by license of the U. S. Federal Trade Commission.

**Acid. Phenylcinch.-Morgenstern.**—A brand of phenylcinchoninic acid, U. S. P.

Manufactured by Morgenstern & Co., New York. No U. S. patent or trademark.

**Tablets Acid. Phenylcinch.-Morgenstern.**—Each tablet contains acid. phenylcinch.-Morgenstern 0.5 Gm. (7.5 grains).

**Sodium Phenylcinch. Water-Morgenstern.**—A solution of sodium phenylcinchoninate containing sodium bicarbonate and sweetened with sugar, representing the equivalent of 1 Gm. (15 grains) acid. phenylcinch.-Morgenstern per fluidounce. It is prepared by dissolving acid. phenylcinch.-Morgenstern 15 Gm., sodium bicarbonate 11.7 Gm., sugar 90 Gm. in water enough to make 450 Cc.

**PHLORIDZIN.**—Phloridzinum.—Phlorizin.—Phlorhizin.— $C_{21}H_{24}O_{10} + 2H_2O$ .—A glucoside from the root of the apple, pear, cherry, etc.

*Actions and Uses.*—Phloridzin destroys malarial parasites. When administered to man or animals, it produces glycosuria of renal origin. Polyuria is also produced. It has been recommended as an antiperiodic in malaria, but its use in this disease is not justified in view of the possible injury to the kidney which it may cause. It is used as a means of testing the functional activity of the kidney.

*Dosage.*—To test the permeability of the kidney 0.005 Gm. ( $\frac{1}{2}$  grain) is dissolved in 1 Cc. (15 minims) of a 0.5 per cent. solution of sodium carbonate and injected hypodermically. Glucose should appear in the urine in from fifteen minutes to one-half hour and the secretion of sugar should continue for from two to four hours. The test gains in diagnostic value if the urine of each kidney is collected separately. Phloridzin may be given by mouth in pills massed with glucose syrup or suspended in a mixture with acacia or tragacanth. The internal dose is from 0.3 to 0.6 Gm. (5 to 10 grains).

Phloridzin occurs as minute white, slightly pinkish crystals, of a silky texture, or as a pale yellow light crystalline powder, odorless and having a bitter but later a sweet taste. It is sparingly soluble in cold, but freely soluble in hot water, from which it loses water and at about 107 C. melts. When heated to about 130 it crystallizes on cooling. It is soluble in alcohol (1:4) and sparingly soluble in ether. The solutions are levogyrate. At 100 C. it becomes solid again and then melts again at about 170 C. At about 200 C. it assumes a red color, due to the formation of rufin. Boiled with dilute acids it is converted into sugar, phlorose and phloretine. Exposed to air in the presence of ammonia it assumes a purple color. Cold concentrated sulphuric acid dissolves it to a yellow solution and at from 25 to 50 C. it becomes red.

**Phloridzin-Merck.**—A nonproprietary brand complying with the standards for phloridzin.

Merck & Co., New York, distributors.

## POLLEN EXTRACTPREPARATIONS

Pollen extracts or pollen protein solutions are aqueous solutions of proteins obtained from the pollen of plants, believed to be the cause of "hay fever."

The Council accepts pollen extracts prepared from the pollen of two or more plants only if in each case a satisfactory reason for the pollen mixture of a particular product is presented. Because of the problematic value of pollen extract the Council accepts such preparations only for a one year period; that is, with the stipulation that the "three year period" of acceptance (see "Duration of Acceptance")

under Explanatory Comments on the Rules) shall not apply.

To avoid confusion and in the interest of rational nomenclature the Council has decided that in the future the term "vaccine" in New and Nonofficial Remedies be restricted to agents which contain living or dead micro-organisms. Under this provision the Council does not accept pollen preparations to which the term "vaccine" is incorrectly applied.

*Actions and Uses.*—Pollen extract is employed for the relief or prophylaxis of a common type of hay fever or pollinosis. Pollen extract prepared from the pollen of one plant (for instance, ragweed) is not primarily intended for use in cases due to pollen from other plants, as grasses and goldenrod, though persons subject to autumn catarrh frequently react to the pollen of more than one species. The patient's susceptibility may be tested by rubbing a small quantity of the pollen extract into a scratch of the skin; if the patient is sensitive to that particular pollen, an urticarial wheal results. To avoid systemic disturbance, it is recommended that no therapeutic injections be made until the reaction from this cutaneous test has subsided completely. Treatment with pollen extract has seemed to give a varying degree of relief in a number of cases. In some cases the psychic element seems to play a part, and in such instances it is difficult to determine to what degree the good results are due to suggestion. The immunity from symptoms conferred by treatment is apparently not permanent, and in most cases does not last longer than a year.

*Dosage.*—It is regarded as important that the individual dosage should be determined by testing each patient's susceptibility, as sensitiveness varies greatly and an overdose may cause disagreeable and alarming symptoms or possibly even death. A method used for such test is to make a series of scratches on the patient's skin (it is important that these should be made at some distance from the scratches of the first test) and to apply to these scratches 25 per cent., 10 per cent., 1 per cent. or even weaker dilutions of the pollen extract. From 5 to 10 drops of the dilution which fails to produce a definite skin reaction may be injected subcutaneously as the first dose. Injections, increasing by a few drops at first, and later by the use of a stronger dilution, may then be given at intervals of a few days or a week.

**HAY FEVER FALL POLLEN EXTRACT-MULFORD.**  
—A liquid obtained by extracting the proteins of the pollen of ragweed (*Ambrosia artemisiaefolia*), golden rod (*Solidago*) and maize (*Zea Mays*), and standardizing the solution by estimating the amount of protein contained in it. Preserved with three cresols.

*Actions and Uses.*—See preceding general article, Pollen Extract Preparations.

*Dosage.*—See preceding general article, Pollen Extract Preparations. Each package of hay fever fall pollen extract-Mulford bears an expiration date (four months from date of removal from laboratory).

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

*Hay Fever Fall Pollen Extract-Mulford, No. 0.*—Four syringe package of hay fever fall pollen extract-Mulford, the syringes containing respectively 0.0025 mg., 0.005 mg., 0.01 mg. and 0.02 mg. of pollen protein.

*Hay Fever Fall Pollen Extract-Mulford, No. 4.*—Twenty Cc. vial of hay fever fall pollen extract-Mulford, each Cc. containing 0.02 mg. of pollen protein.

*Hay Fever Fall Pollen Extract-Mulford, No. 9.*—Five Cc. vial of hay fever fall pollen extract-Mulford, each Cc. containing 0.02 mg. of pollen protein.

*Hay Fever Fall Pollen Extract-Mulford, No. 11.*—One syringe package of hay fever fall pollen extract-Mulford, containing 0.02 mg. of pollen protein.

*Hay Fever Fall Pollen Extract-Mulford, No. 12.*—One syringe package of hay fever fall pollen extract-Mulford, containing 0.04 mg. of pollen protein.

*Hay Fever Fall Pollen Extract-Mulford, No. 14.*—One syringe package of hay fever fall pollen extract-Mulford, containing 0.08 mg. of pollen protein.

A mixture of 90 parts of the pollen of ragweed, 5 parts of the pollen of various species of golden rod and 5 parts of the pollen of maize after being dried is ground in a ball-mill to destroy the cell membrane. It is then extracted with physiologic sodium chloride solution. This extract is precipitated with acetone. The precipitate is dried and finally extracted again with physiologic sodium chloride solution. The soluble proteins being brought into solution, a nitrogen determination is made on this extract, and it is then standardized according to the protein (nitrogen) content.

**HAY FEVER RAGWEED POLLEN EXTRACT-MULFORD.**—A liquid obtained by extracting the proteins from the pollen of ragweed (*Ambrosia artemisiaefolia*), and standardizing the solution by estimating the amount of protein contained in it. Preserved with three cresols.

*Actions and Uses.*—See preceding general article, Pollen Extract Preparations.

*Dosage.*—See preceding general article, Pollen Extract Preparations. Each package of hay fever ragweed pollen extract-Mulford bears an expiration date (four months from date of removal from laboratory).

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

*Hay Fever Ragweed Pollen Extract-Mulford, No. 0.*—Four syringe package of hay fever ragweed pollen extract-Mulford, the syringes containing respectively 0.0025 mg., 0.005 mg., 0.01 mg. and 0.02 mg. of pollen protein.

*Hay Fever Ragweed Pollen Extract-Mulford, No. 4.*—Twenty Cc. vial of hay fever ragweed pollen extract-Mulford, each Cc. containing 0.02 mg. of pollen protein.



*Hay Fever Ragweed Pollen Extract-Mulford, No. 9.*—Five Cc. vial of hay fever ragweed pollen extract-Mulford, each Cc. containing 0.02 mg. of pollen protein.

*Hay Fever Ragweed Pollen Extract-Mulford, No. 11.*—One syringe package of hay fever ragweed pollen extract-Mulford, containing 0.02 mg. of pollen protein.

*Hay Fever Ragweed Pollen Extract-Mulford, No. 12.*—One syringe package of hay fever ragweed pollen extract-Mulford, containing 0.04 mg. of pollen protein.

*Hay Fever Ragweed Pollen Extract-Mulford, No. 14.*—One syringe package of hay fever ragweed pollen extract-Mulford, containing 0.08 mg. of pollen protein.

The pollen, after being dried, is ground in a ball-mill to destroy the cell membrane. It is then extracted with physiologic sodium chloride solution. This extract is precipitated with acetone. The precipitate is dried and finally extracted again with physiologic sodium chloride solution. The soluble proteins being brought into solution, a nitrogen determination is made of this extract, and it is then standardized according to the protein (nitrogen) content.

**HAY FEVER SPRING POLLEN EXTRACT-MULFORD.**—A liquid obtained by extracting the proteins of the pollen of rye (*Secale cereale*), timothy (*Phleum pratense*), orchard grass (*Dactylis glomerata*), sweet vernal grass (*Anthoxanthum odoratum*), and red top grass (*Agrostis alba*), and standardizing the solution by estimating the amount of protein contained in it. Preserved with three cresols.

*Actions and Uses.*—See preceding general article, Pollen Extract Preparations.

*Dosage.*—See preceding general article, Pollen Extract Preparations. Each package of hay fever spring pollen extract-Mulford bears an expiration date (four months from date of removal from laboratory).

Manufactured by the H. K. Mulford Company, Philadelphia. No U. S. patent or trademark.

*Hay Fever Spring Pollen Extract-Mulford, No. 0.*—Four syringe package of hay fever spring pollen extract-Mulford, the syringes containing respectively 0.0025 mg., 0.005 mg., 0.01 mg., and 0.02 mg. of pollen protein.

*Hay Fever Spring Pollen Extract-Mulford, No. 4.*—Twenty Cc. vial of hay fever spring pollen extract-Mulford, each Cc. containing 0.02 mg. of pollen protein.

*Hay Fever Spring Pollen Extract-Mulford, No. 9.*—Five Cc. vial of hay fever spring pollen extract-Mulford, each Cc. containing 0.02 mg. of pollen protein.

*Hay Fever Spring Pollen Extract-Mulford, No. 11.*—One syringe package of hay fever spring pollen extract-Mulford, containing 0.02 mg. of pollen protein.

*Hay Fever Spring Pollen Extract-Mulford, No. 12.*—One syringe package of hay fever spring pollen extract-Mulford, containing 0.04 mg. of pollen protein.

*Hay Fever Spring Pollen Extract-Mulford, No. 14.*—One syringe package of hay fever spring pollen extract-Mulford, containing 0.08 mg. of pollen protein.

Equal parts of the pollen of rye (*Secale cereale*), timothy (*Phleum pratense*), orchard grass (*Dactylis glomerata*), sweet vernal grass (*Anthoxanthum odoratum*), and red top grass (*Agrostis alba*) after being dried are ground in a ball-mill to destroy the cell membrane. This is then extracted with physiological sodium chloride solution. The extract is precipitated with acetone. The precipitate is dried and finally extracted again with physiological sodium chloride solution. The soluble proteins being brought into solution, a nitrogen determination is made on this extract, and it is then standardized according to the protein (nitrogen) content.

## PYRAZOLON DERIVATIVES

The preparations in this group are used for their antipyretic and analgesic action. There is reason to believe that they have less tendency to disintegrate the red blood-corpuscles than the phenetidine compounds, but in other respects they are open to the same objections. In small doses some susceptible individuals experience nervous and circulatory depression, while after large doses instances of collapse have been reported.

The following pyrazolon derivatives are included in New and Nonofficial Remedies:

Antipyrine salicylate (salipyrine), which is a simple salt of antipyrine with salicylic acid, said to possess the therapeutic properties of both these constituents.

Melubrin, a complex synthetic differing from antipyrine in that a sodium amino-methan-sulphonate has replaced the hydrogen atom of the pyrazolon group. In this it is asserted that the toxicity is very much reduced.

Dimethylaminoantipyrine (pyramidon).

## Antipyrine Compounds and Derivatives

Antipyrine, phenyldimethylpyrazolon, is a weak base which unites with acids to form unstable salts that hydrolyze readily when dissolved in water, separating into the components. The therapeutic activity of these compounds represents a combination of the actions of the acid and the base.

**SALIPYRINE.**—Antipyrinæ Salicylas.—Antipyrine Salicylate.— $C_{11}H_{12}N_2O.C_6H_4OH.CO_2H$ .—A weak chemical combination of antipyrine and salicylic acid.

**Actions and Uses.**—This compound possesses the properties of both antipyrine and salicylic acid and combines the analgesic power of the one with the antirheumatic action of the other. It has been used with good results in sciatica, rheumatic fever, chronic rheumatism, influenza, pleurisy, dysmenorrhœa, etc.

**Dosage.**—From 0.3 to 2 Gm. (5 to 30 grains) in cachets or capsules.

Manufactured by J. D. Riedel, Aktiengesellschaft, Berlin, Germany (Riedel & Co., New York). U. S. patent expired. U. S. trademark No. 76,952.



is claimed that as much as 10 Gm. (150 grains) may be given daily.

Manufactured by Farbwerke, vorm. Meister, Lucius & Bruening, Hoechst, a. M., Germany (H. A. Metz Laboratories, Inc., New York). U. S. patent No. 1,056,881 (March 5, 1913; expires 1930). U. S. trademark applied for.

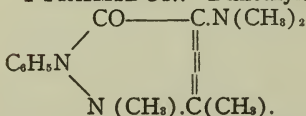
Melubrin is prepared by allowing a solution of formaldehyde bisulphite to act on 1-phenyl-2,3-dimethyl-4-amino-pyrazolon, and purifying the resulting product by recrystallization.

It is a white, odorless, almost tasteless crystalline powder, readily soluble in water, but slightly soluble in alcohol. The aqueous solution is neutral in reaction but unstable.

If about 0.2 Gm. of melubrin dissolved in 5 Cc. of water be boiled with 3 Cc. of diluted hydrochloric acid, sulphur dioxide and formaldehyde will be liberated. If half of the solution thus formed be treated with 3 drops of sodium nitrite solution and 5 Cc. of an alkaline solution of betanaphthol, a red precipitate will be produced. If the remainder of the solution be treated with 1 Gm. of sodium acetate and 15 Cc. of a saturated aqueous benzaldehyde solution, a yellowish white, flocculent precipitate will be formed which, when washed and dried, will melt at 173 C. If a small quantity of melubrin be moistened with hydrochloric acid, it will respond to the flame test for sodium. If a 10 per cent. aqueous solution of melubrin be made alkaline with ammonia, saturation with hydrogen sulphide should produce no change. If 0.5 Gm. of melubrin be thoroughly mixed with 4 Gm. of sodium nitrate and gradually heated, 4 Cc. of concentrated sulphuric acid added to the resulting mass, and the mixture heated till no further white fumes are produced, the resulting substance powdered and mixed with 10 Cc. of saturated hydrochloric acid solution of stannous chloride, no darkening should occur within one hour. If 0.4 to 0.5 Gm. of melubrin be weighed to a platinum dish, treated with dilute sulphuric acid, and heated to constant weight, the sodium sulphate thus formed should weigh 0.2160 to 0.2250 Gm. for each Gm. of material used, representing a sodium content of 6.99 to 7.28 per cent.

### Pyramidon and Pyramidon Compounds

**PYRAMIDON.**—Dimethylaminoantipyrina.—



Phenyl-dimethyl-dimethylamino-pyrazolon, differing from antipyrine,  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$ , in that a dimethylamino group,  $\text{N}(\text{CH}_3)_2$ , has replaced a hydrogen atom of the pyrazolon nucleus.

*Actions and Uses.*—Pyramidon acts as an antipyretic and anodyne, like antipyrine, but is effective in smaller doses. The action, while somewhat slower at the beginning, is more lasting. It is claimed to be comparatively free from harmful influences on the blood, heart or kidneys. It is said to be useful, particularly in the chronic fevers of tuberculosis, as



well as in the acute febrile conditions incident to typhoid fever, erysipelas and pneumonia. In the treatment of infectious fevers, it, like other antipyretics, should be cautiously employed. See general article, Phenetidin Derivatives.

*Dosage.*—From 0.3 to 0.4 Gm. (5 to 6 grains), most conveniently in the form of tablets, a single dose usually sufficing for twenty-four hours.

Manufactured by Farbwerke, vorm. Meister, Lucius & Bruening, Hoechst a. M., Germany (H. A. Metz Laboratories, Inc., New York). U. S. patent expired.

Pyramidon is prepared by the reduction of nitroso-antipyrine to amino-antipyrine and treating this with methyl chloride or iodide.

It forms small, colorless, slightly alkaline crystals, melting at 108 C.; almost tasteless; soluble in 11 parts of cold water and readily soluble in alcohol, ether and benzene. Its aqueous solution saturated at 70 C. deposits oily globules of pyramidon on boiling.

Ferric chloride colors the neutral or slightly acidulated solution of pyramidon a bluish violet color; nitrous or nitric acid produces a fugitive blue-violet color; silver nitrate produces an intense violet coloration when added to the aqueous solution, followed by the formation of a black precipitate of metallic silver, and the same color is produced by platinum chloride, by ammonium persulphate and by lead dioxide. In hydrochloric acid solution pyramidon gives a fine crystalline double salt with mercuric chloride.

Its incompatibilities are in general the same as those of antipyrine. Oxidizing agents (also acacia) often produce colored solutions.

## QUININE DERIVATIVES

The action of quinine is essentially the same in all its compounds. The official salts have the disadvantage of the bitter taste, and of producing a local action on the stomach and other tissues. To obviate these difficulties, insoluble compounds like the alkaloid or the tannate have been used, since these pass the mouth and stomach without offending the taste or disturbing the stomach. The same object is attained more or less completely in a number of synthetic compounds in which the quinine radicle is combined with other radicles, such as those of carbonic acid, to form tasteless and insoluble esters. In the intestines these esters are broken up more or less rapidly into the alkaloid quinine and their other components. The rapidity with which this decomposition occurs will determine to a large extent the intensity of the therapeutic effect and the liability to produce cinchonism.

Some of the esters also contain other therapeutically active radicals (phenetidine, salicyl, etc.). When liberated these produce their proper effects; but it is doubtful whether the combinations of several therapeutically active radicles in fixed proportions are superior to simple mixtures of the ingredients.

The irritant action and the relatively low solubility of most of the ordinary quinine salts interferes with their use for hypodermic injection or local anesthesia. This difficulty has

been met by the introduction of double salts of quinine with certain organic substances, especially the quinine-urea hydrochloride.

The following quinine compounds are included in N. N. R.:

Soluble salts: quinine and urea hydrochloride and quinine dihydrochloride.

Insoluble salt: quinine tannate.

**QUININE DIHYDROCHLORIDE.**—For description see the U. S. Pharmacopeia under *Quininae Dihydrochloridum*.

**Quinine Dihydrochloride-Merck.**—A brand of quinine dihydrochloride, U. S. P.

Merck & Co., New York, distributors.

*Ampuls Quinine Dihydrochloride-Mulford, 0.24 Gm.*—Each ampule contains 0.24 Gm. ( $3\frac{3}{4}$  grains) quinine dihydrochloride in 1 Cc. of sterile solution. Prepared by H. K. Mulford Co., Philadelphia.

*Ampuls Quinine Dihydrochloride-Mulford, 0.5 Gm.*—Each ampule contains 0.5 Gm. ( $7\frac{3}{4}$  grains) quinine dihydrochloride in 1 Cc. of sterile solution. Prepared by H. K. Mulford Co., Philadelphia.

*Ampuls Quinine Dihydrochloride-Squibb, 1 Gm.*—Each ampule contains quinine dihydrochloride 1 Gm. ( $15\frac{1}{2}$  grains) in 2 Cc. of sterile solution. Prepared by E. R. Squibb & Sons, New York.

*Ampuls Quinine Dihydrochloride-Squibb, 0.5 Gm.*—Each ampule contains quinine dihydrochloride 0.5 Gm. ( $7\frac{1}{2}$  grains) in 2 Cc. of sterile solution. Prepared by E. R. Squibb & Sons, New York.

*Ampuls Quinine Dihydrochloride-Squibb, 0.25 Gm.*—Each ampule contains quinine dihydrochloride 0.25 Gm. ( $3\frac{3}{4}$  grains) in 2 Cc. of sterile solution. Prepared by E. R. Squibb & Sons, New York.

**QUININE ETHYL CARBONATE-MERCK.**—*Quininae Æthylcarbonas.*—Euquinine.— $C_2H_5O.CO.O.C_{20}H_{28}N_2O$ .—The quinine ester of ethyl carbonic acid. First introduced as euquinine.

*Actions and Uses.*—Those of a nearly tasteless and insoluble quinine compound.

*Dosage.*—The same as quinine.

Merck & Co., New York, distributors. No. U. S. patent or trademark.

*Quinine Ethyl Carbonate-Merck Tablets, 2 grains.*—Each tablet contains quinine ethyl carbonate-Merck 2 grains.

It occurs as a light, fleecy conglomeration of delicate white needles, which are practically tasteless.

It is sparingly soluble in water, but readily soluble in alcohol, ether and chloroform.

It is slightly alkaline in reaction, forming well crystallizable, bitter salts with acids.

Quinine ethyl carbonate melts at 89 to 91 C.

Dissolve about 0.2 Gm. of quinine ethyl carbonate in 5 Cc. of dilute sulphuric acid and dilute to 50 Cc. The solution exhibits a strong blue fluorescence, and responds to the general tests for alkaloids. Add 2 or 3 drops of bromine test solution to a 1 Cc. portion of the solution followed by 1 Cc. of ammonia water; the liquid acquires an emerald green color due to the formation of thalleoquin.

Dissolve 0.2 Gm. of quinine ethyl carbonate in 5 Cc. of nitric acid and dilute to 25 Cc. To a 5 Cc. portion add 1 Cc. silver nitrate test solution. No precipitate is formed (*chloride*). To another 5 Cc. portion add 1 Cc. barium chloride test solution. No precipitate is formed (*sulphate*).

Add 5 Cc. of iodine test solution to about 0.2 Gm. of quinine ethyl carbonate, decolorize with sodium hydroxide test solution and warm. The odor of iodoform is manifested (*ethyl group*).

Incinerate about 0.5 Gm., accurately weighed. Not more than 0.1 per cent. of residue remains.

**QUININE TANNATE.**—For description see the U. S. Pharmacopeia under *Quininae Tannas*.

*Actions, Uses and Dosage.*—See Useful Drugs.

**Quinine Tannate-Merck.**—A nonproprietary brand complying with the standards for quinine tannate.

Merck & Co., New York, distributors.

**Quinine Tannate-N. Y. Q.**—A nonproprietary brand complying with the standards for quinine tannate.

Manufactured by the New York Quinine and Chemical Works, New York.

**Quinine Tannate-Brunswick.**—A nonproprietary brand complying with the standards for quinine tannate.

Manufactured by the Brunswick Chemical Works, Brunswick, Germany (Mallinckrodt Chemical Works, St. Louis).

**Quinine Tannate-P. W. R.**—A nonproprietary brand complying with the standards for quinine tannate.

Manufactured by Powers-Weightman-Rosengarten Co., Philadelphia.

**QUININE AND UREA HYDROCHLORIDE.**—For description see the U. S. Pharmacopeia under *Quininae et Ureae Hydrochloridum*.

*Actions and Uses.*—Quinine and urea hydrochloride has the actions of quinine but is relatively nonirritating. When injected hypodermically or when applied locally to mucous membranes it exerts an anesthetic action similar to that of cocaine, which, however, may last for several days. It is reported that the anesthesia is in some cases prolonged for several days.

Quinine and urea hydrochloride is used in the treatment of malaria by hypodermic injections. It has also been applied as a substitute for cocaine in the production of local anesthesia for operations.

*Dosage.*—The same as quinine. For the production of local anesthesia injections of a solution of from 0.25 to 1 per cent. strength are used. The 0.25 per cent. solution is said to be

free from the risk of producing fibrous indurations, which sometimes occurs with the stronger solution. For application to mucous membranes solutions varying in strength from 10 to 20 per cent. should be used.

**Quinine and Urea Hydrochloride-Merck.**—A brand of quinine and urea hydrochloride, U. S. P.

Merck & Co., New York, distributors.

*Ampuls Quinine and Urea Hydrochloride (1%)-Mulford.* — Each ampule contains 5 Cc. of a sterile 1 per cent. solution of quinine and urea hydrochloride. Prepared by H. K. Mulford Co., Philadelphia.

*Ampuls Quinine and Urea Hydrochloride-Squibb, 1 Gm.* — Each ampule contains quinine and urea hydrochloride 1 Gm. (15½ grains) in 2 Cc. of sterile solution. Prepared by E. R. Squibb & Sons, New York.

*Ampuls Quinine and Urea Hydrochloride-Squibb, 0.5 Gm.* — Each ampule contains quinine and urea hydrochloride 0.5 Gm. (7½ grains) in 2 Cc. of sterile solution. Prepared by E. R. Squibb & Sons, New York.

*Ampuls Quinine and Urea Hydrochloride-Squibb, 0.25 Gm.* — Each ampule contains quinine and urea hydrochloride 0.25 Gm. (3¾ grains) in 2 Cc. of sterile solution. Prepared by E. R. Squibb & Sons, New York.

*Ampuls Quinine and Urea Hydrochloride-Squibb, 1 per cent.* — Each ampule contains 5 Cc. of a sterile 1 per cent. solution of quinine and urea hydrochloride. Prepared by E. R. Squibb & Sons, New York.

## RADIUM AND RADIUM SALTS

Radium is a bivalent metallic element closely related to barium. It is exceedingly reactive, making it difficult to isolate in its metallic state and after isolation to keep in a pure state, as it reacts with air, forming the oxide and nitride, and finally the carbonate. On account of this activity it is produced only in the form of its salts, principally as the bromide, chloride, sulphate and carbonate.

The most important property of radium is its radio-activity on which depends its therapeutic value. Radio-activity is defined as "the property of spontaneously emitting radiations part of which are capable of passing through plates of metal and other substances opaque to ordinary light and having the power of discharging electrified bodies." A spontaneous disintegration of the atoms characterizes all the radio-active elements and it is in this transmutation or splitting of the atom that the rays are shot out, some being material in nature, others electrical or of the nature of light. This spontaneous transmutation of radium is going on at a regular rate, which is independent of the state of combination of radium in the molecule of its compounds.

Radium is changing at such a rate that in 2,000 years about half of any quantity will have changed. Radium emanation decays much more rapidly, and in 3.85 days any quan-



tity of the emanation will fall to half its initial activity, owing to disintegration of the atoms.

To determine the radio-active value of radium, use is made of its property of ionizing gases. Thus when radium is allowed to act on the air in a charged gold-leaf electroscope the air becomes ionized and therefore a conductor of electricity and allows the charge to leak away, causing the leaf in the electroscope to move. By observing the rate of movement of the leaf in a calibrated apparatus the radio-activity can be determined.

For the valuation of radium preparations the Council uses the standard promulgated by the International Commission on Radium Standards as applied by the Bureau of Standards of the United States Department of Commerce. The Council advises purchasers of large quantities of radium to have the purchased products examined by the Bureau of Standards of the United States Department of Commerce.

Radium preparations are valuable in proportion to their content of radium. The content of radium may be found with a high degree of accuracy by two distinct methods: (1) by means of measurement of its gamma rays; (2) by means of measurement of its emanation.

The first method consists in the measurement of the rate of discharge of an electroscope by the gamma rays which have passed through a sheet of lead 1 cm. in thickness. The result gives the number of milligrams of radium element present in the sample and is accurate to a fraction of 1 per cent. This method is not suitable for quantities of radium of less than 0.1 mg.

The emanation method is used for radium solutions, either strong or very weak and also for the determination of the radium content of slightly active solids; in the latter case it is first necessary to bring the substance into solution by suitable methods. The activity of the emanation, obtained under definite conditions from the solution to be analyzed, is compared by means of an emanation electroscope with the activity of the emanation from a standard radium solution. From the results the quantity of radium element present in the preparation may be computed. In the foregoing methods of measuring solutions of radium salts, due precautions (such as boiling) must be taken in order that the measurement shall represent the *actual* radium content. Both of the foregoing are official methods of the Bureau of Standards.

The measurements of the amounts of *radium element* or *radium emanation* may be expressed in the following units:

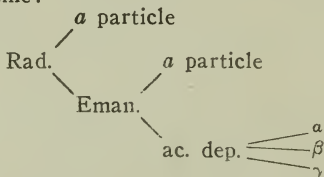
1. Milligrams, or fractions of a milligram, of *radium element* present.
2. Micrograms, or fractions of a microgram, of *radium element* present, a microgram being 0.001 milligram.
3. (a) Curies, or fractions of a curie, of *radium emanation*, the curie being standardized as the maximum quantity of

emanation given off by one gram of radium element; (b) Microcuries, or fractions of microcuries of radium *emanation*, the microcurie being standardized as the maximum emanation from one microgram (0.001 milligram) of radium element.

4. Mache units: It is generally considered that 2,700 Mache units expresses the equivalent of one microcurie of radium *emanation*. The use of the term of measurement of radium emanation should be discouraged because (1) a number of definitions for this unit are in use; (2) the term properly applied denotes concentration rather than quantity.

The first two modes of expression are used in reporting analysis of the actual radium content in radium preparations. The third mode expresses the radium emanation; properly used a curie may express the radium element content, but on the other hand it may express only the emanation content and be no indication of the radium element content. Hence it should be used only to denote emanation concentration from radioactive generators, etc. The analysis is usually accurate to 1 per cent. even when as little as 0.0001 mg. of radium is present, while one millionth of a milligram can be detected with certainty.

*Relation of Radium, Radium Emanation and Rays.*—A large part of the rays are derived indirectly from radium through the formation of its "active deposit," according to the following scheme:



These rays are divided into three groups, the alpha, beta and gamma, which differ in their velocity and penetrative power. The alpha rays consist of minute particles of matter; in fact, of electro-positively charged atoms of helium; the beta rays are particles of negative electricity, the so-called electrons. Both kinds of rays have enormous velocities, approaching the velocity of light. The alpha rays are feebly penetrating, being stopped by a sheet of paper. These rays are the most powerfully ionizing of the three sorts. The beta rays are more penetrating than the alpha rays, being able to produce effects through several thicknesses of paper or very thin sheets of metal or glass. The gamma rays are vibrations in the ether, very similar to roentgen-rays, and of high penetrating power. Therapeutically the last group is the most useful.

Radium emanation is continuously given off from aqueous solutions of radium salts. It can be collected as it escapes from the solution, from which it is completely expelled by

boiling, drawn off through the use of the mercury pump, or by other suitable means, quantitatively determined by its action on the electroscope, brought into solution in water for internal or external use or be set free in an emanatorium for inhalation treatment. It may be collected in small glass containers and this used in place of the applicators described under surgical use.

*Actions and Uses.*—Solutions of radium or radium emanation are said to increase the excretion of uric acid in the urine in some cases and to decrease its concentration in the blood; to increase somewhat the number of red blood-corpuscles; to cause temporary leukocytosis early in the course of treatment, the mononuclear increase being relatively greater; to lead frequently through long-continued use to leukopenia, although no appreciable benefit is observed in leukemia. It is said that radium increases general metabolism, and *in vitro* activates certain enzymes, pepsin, pancreaticin, rennin, autolytic ferments, tyrosinase and diastase.

It has been claimed that radium emanation is of value in all forms of nonsuppurative, acute, subacute and chronic arthritis (luetic and tuberculous excepted), in chronic muscle and joint rheumatism (so-called), in arthritis deformans, in acute and chronic gout, in neuralgia, sciatica, lumbago, and in tabes dorsalis for the relief of lancinating pains. Its chief value is in the relief of pain.

The relief of pain is well established; in consequence, improvement is sometimes observed but curative results appear to be lacking. Due conservatism should be exercised in judging of the favorable reports published.

Physicians should realize that the emanation following the administration of an emanation solution (such as that from radio-active water generators) is very soon lost from the body (a large portion also escapes during the process of drinking) whereas a radium solution leaves a large part of its radium content in the system to be slowly excreted in the course of several months. For this reason, radium solutions produce a condition of radio-activity in the body for a longer period than emanation preparations. It is not desirable therefore to consider an emanation solution containing a certain amount of emanation as equivalent therapeutically to a radium solution which is capable of producing the same equilibrium amount of emanation.

*Surgical Use.*—Nearly all pathologic tissues are more sensitive than normal tissues. There is, however, a wide variation in the normal tissues; for instance, the ovary and the other sexual organs are very sensitive; the eye and the nervous tissues are very insensitive. In certain new growths, both benign and malignant, a favorable influence is exerted. Of the malignant growths the best results have been obtained with sarcomas, especially lymphosarcomas.

In skin diseases marked results are obtained with epitheliomas, birthmarks and scars.

There is a sedative effect in true neuralgias as well as those due to tumor pressure.

*Technic.*—The efficiency of the treatment is due to the beta and gamma rays. The quantity of radiation is proportional to the amount of radium element represented in the salt or the emanation. Pure gamma rays may be employed when the apparatus is surrounded by at least 3 mm. of lead.

The technic of filtration of the rays by the use of suitable metallic or other screens, of the length of application and of the amount is still in the experimental stage. Treatment by radium salts should be in the hands only of experts. The radium salts and the emanation can be placed in any sealed container, but preferably in glass.

*Dosage.*—Radium may be administered as baths, by subcutaneous injection in the neighborhood of an involved joint (0.25 to 0.5 microgram in 1 or 2 Cc. distilled water), by local application as compresses (from 5 to 10 micrograms), by mouth as a drink cure (in increasing doses of from 1 to 10 micrograms three or more times a day), by drinking radioactive water, containing only radium emanation (from 2 to 20 microcuries of emanation, or more in twenty-four hours), by inhalation of the emanation, the patient for two hours daily remaining in the emanatorium which contains 0.0025 to 0.25 (average 0.1) microcurie of emanation per liter of air. The Council will not accept any radium solution for internal use, the dosage of which is less than 2 micrograms per day, nor any radium emanation generator which yields less than 2 microcuries of emanation per twenty-four hours.

**RADIUM BROMIDE.**— $\text{RaBr}_2$ .—The anhydrous radium salt of hydrobromic acid.—The market supply is usually a mixture of radium bromide and barium bromide and is sold on the basis of its radium content.

*Actions and Uses.*—See Radium.

*Dosage.*—See Radium.

Pure anhydrous radium bromide, containing 58.6 per cent. of radium (Ra), is a white or slightly brownish crystalline substance, soluble in water.

The presence of radium can qualitatively be demonstrated by electroscopic or by photographic methods.

The quantitative determination of radium is carried out according to the method of Rutherford and Boltwood (Rutherford's "Radio-Active Substances and their Radiations," Cambridge, 1913).

**Radium Bromide, W. L. Cummings Chemical Co.**—

Supplied in the form of a mixture of radium bromide and barium bromide. All deliveries are made subject to the tests of the U. S. Bureau of Standards.



Manufactured by the W. L. Cummings Chemical Co., Lansdowne, near Philadelphia, Pa.

**Radium Bromide, Radium Company of Colorado, Inc.**—Supplied in the form of a mixture of radium bromide and barium bromide. All deliveries are made subject to the tests of the U. S. Bureau of Standards.

Manufactured by the Radium Company of Colorado, Inc., Denver, Colo.

**Radium Bromide, Standard Chemical Co.**—Supplied in the form of a mixture of radium bromide and barium bromide.

Manufactured by the Standard Chemical Co., Pittsburgh (The Radium Chemical Co., Pittsburgh).

**RADIUM CARBONATE.** —  $\text{RaCO}_3$ . — The anhydrous radium salt of carbonic acid.—The market supply is usually a mixture of radium carbonate and barium carbonate and is sold on the basis of its radium content.

*Actions and Uses.*—See Radium.

*Dosage.*—See Radium.

Pure radium carbonate, containing 79.0 per cent. of radium (Ra), is a white or slightly brownish salt insoluble in water, decomposed by acids.

No gases are given off spontaneously from anhydrous radium carbonate by reason of the decomposing action of the radiations, as is the case with the chloride and bromide.

The presence of radium can be demonstrated qualitatively by electroscopic or by photographic methods.

The quantitative determination of radium is carried out according to the method of Rutherford and Boltwood (Rutherford's "Radioactive Substances and their Radiations").

**Radium Carbonate, W. L. Cummings Chemical Co.**—

Supplied in the form of a mixture of radium carbonate and barium carbonate. All deliveries are made subject to the tests of the U. S. Bureau of Standards.

Manufactured by the W. L. Cummings Chemical Co., Lansdowne, near Philadelphia, Pa.

**Radium Carbonate, Radium Company of Colorado, Inc.**—

Supplied in the form of a mixture of radium carbonate and barium bromide. All deliveries are made subject to the tests of the U. S. Bureau of Standards.

Manufactured by the Radium Company of Colorado, Inc., Denver, Colo.

**Radium Carbonate, Standard Chemical Co.**—Supplied in the form of a mixture of radium carbonate and barium carbonate.

Manufactured by the Standard Chemical Co., Pittsburgh (Radium Chemical Co., Pittsburgh).

**RADIUM CHLORIDE.**— $\text{RaCl}_2$ .—The anhydrous radium salt of hydrochloric acid. The market supply is usually a mixture of radium chloride and barium chloride and is sold on the basis of its radium content.

*Actions and Uses.*—See Radium.

*Dosage.*—See Radium.

Pure anhydrous radium chloride, containing 76.1 per cent. radium (Ra), is a white or slightly brownish crystalline substance, soluble in water.

The presence of radium can qualitatively be demonstrated by electroscopic or by photographic methods. The quantitative determination of radium is carried out according to the method of Rutherford and Boltwood (Rutherford's "Radioactive Substances and their Radiations").

**Radium Chloride, W. L. Cummings Chemical Co.**—

Supplied in the form of a mixture of radium chloride and barium chloride. All deliveries are made subject to the tests of the U. S. Bureau of Standards.

Manufactured by the W. L. Cummings Chemical Co., Lansdowne, near Philadelphia, Pa.

**Radium Chloride, Radium Company of Colorado, Inc.**—

Supplied in the form of a mixture of radium chloride and barium bromide. All deliveries are made subject to the tests of the U. S. Bureau of Standards.

Manufactured by the Radium Company of Colorado, Inc., Denver, Colo.

**Radium Chloride, Standard Chemical Co.**—Supplied in the form of a mixture of radium chloride and barium chloride.

Manufactured by the Standard Chemical Co., Pittsburgh (The Radium Chemical Co., Pittsburgh).

**RADIUM SULPHATE.**— $\text{RaSO}_4$ .—The anhydrous radium salt of sulphuric acid. The market supply is usually a mixture of radium sulphate and barium sulphate and is sold on the basis of its radium content.

*Actions and Uses.*—See Radium.

*Dosage.*—See Radium.

Pure radium sulphate, containing 70.2 per cent. radium (Ra), is a white substance insoluble in water and dilute acids.

The presence of radium can be demonstrated qualitatively by electroscopic or by photographic methods.

The quantitative determination of radium is carried out according to the method of Rutherford and Boltwood (Rutherford's "Radio-active Substances and their Radiations").

#### Radium Sulphate, W. L. Cummings Chemical Co.—

Supplied in the form of a mixture of radium sulphate and barium sulphate. All deliveries are made subject to the tests of the U. S. Bureau of Standards.

Manufactured by the W. L. Cummings Chemical Co., Lansdowne, near Philadelphia, Pa.

#### Radium Sulphate, Radium Company of Colorado, Inc.—

Supplied in the form of a mixture of radium sulphate and barium bromide. All deliveries are made subject to the tests of the U. S. Bureau of Standards.

Manufactured by the Radium Company of Colorado, Inc., Denver, Colo.

Radium Sulphate, Standard Chemical Co.—Supplied in the form of a mixture of radium sulphate and barium sulphate.

Manufactured by the Standard Chemical Co., Pittsburgh (The Radium Chemical Co., Pittsburgh).

**RADIO-REM.**—An apparatus designed for the production of radioactive drinking water by impregnating the water with radium emanation emitted from radium sulphate which is contained in fired porous clay plates. (The exact efficiency is stated and guaranteed at the time of sale.)

*Actions, Uses and Dosage.*—See general article on radium.

Radium Therapy Corporation, New York (Schieffelin and Co., New York). U. S. patent Nos. 1,032,951 and 1,032,779 (July 16, 1912; expire 1929). U. S. trademark No. 99,507.

*Radio-Rem, Outfit No. 4.*—An apparatus which imparts 1.8 microcurie (5,000 Mache units) to 500 Cc. water daily; that is, each plate is designed to impart about 0.9 microcurie (2,500 Mache units) to the water which fills the bottle, in twenty-four hours.

*Radio-Rem, Outfit No. 5.*—An apparatus which imparts about 3.6 microcurie (10,000 Mache units) to 500 Cc. water daily; that is, each plate is designed to impart about 1.8 microcurie (5,000 Mache units) to the water which fills the bottle, in twenty-four hours.

Each of the above-described Radio-Rem Outfits consists of two wide-mouthed glass-stoppered bottles of about 250 Cc. capacity, each containing a fired, porous clay (terra cotta) plate, said to contain radium sulphate. The efficiency of each tablet is given at the time of sale; the manufacturers agree to replace the tablets and to pay for the test, if examination by the U. S. Bureau of Standards shows them to be deficient.

A test made for the Council demonstrated that during the impregnation of the water with radium emanation, no radium is dissolved in the water, the radio-activity being due to the presence of the emanation.

#### SAUBERMANN RADIUM EMANATION ACTIVATOR.

—An apparatus for the production of radio-active drinking water by impregnating the water with emanations emitted from radium sulphate which is contained in a porcelain cylinder.

*Actions, Uses and Dosage.*—See preceding general article on radium.

Manufactured by Radium, Limited, U. S. A., New York. U. S. patent applied for. U. S. trademark No. 105,488.

*Saubermann Radium Emanation Activator, 5,000 Mache Units.*—An apparatus which imparts about 1.8 microcurie (5,000 Mache units) to about 500 Cc. water daily. Each apparatus is accompanied by a statement of its daily capacity and efficiency.

*Saubermann Radium Emanation Activator, 10,000 Mache Units.*—An apparatus which imparts about 3.6 microcurie (10,000 Mache units) to about 500 Cc. water daily. Each apparatus is accompanied by a statement of its daily capacity and efficiency.

*Saubermann Radium Emanation Activator, 20,000 Mache Units.*—An apparatus which imparts about 7.2 microcurie (20,000 Mache units) to about 500 Cc. water daily. Each apparatus is accompanied by a statement of its daily capacity and efficiency.

*Saubermann Radium Emanation Activator, 50,000 Mache Units.*—An apparatus which imparts about 18 microcurie (50,000 Mache units) to about 500 Cc. water daily. Each apparatus is accompanied by a statement of its daily capacity and efficiency.

Each Saubermann radium emanation activator consists of three parts, two being glass vessels with a ground glass joint, the third being a porcelain cylinder containing radium sulphate. The larger glass part holds about 2,000 Cc. of water when the porcelain cylinder is in place. The smaller glass part has a capacity of about 500 Cc. For use the apparatus is filled with water and the contents of the smaller vessel are drawn off at intervals of twenty-four hours.

An examination of two generators made for the Council demonstrated that during the impregnation of the water with radium emanation for twenty-four hours, respectively, 0.035 and 0.077 microgram of radium element was dissolved in each 500 Cc.

**STANDARD RADIUM COMPRESS.**—A compress containing 225 Gm. (8 ounces) of a mixture consisting chiefly of silica, barium sulphate containing radium sulphate equivalent to 15 micrograms (0.015 mg.) of radium element.

*Actions and Uses.*—See Radium. Being applied wet, it is claimed that the action of Standard radium compress is partly due to beta and gamma radiation of the finely divided insoluble radium salts and partly to the radium emanation which is dissolved out by the water.



*Dosage.*—See Radium. The amount of radium being small, it is claimed that the compress can be applied for a long period of time without danger of inflammation or necrosis.

Manufactured by the Standard Chemical Co., Pittsburgh (The Radium Chemical Co., Pittsburgh). No U. S. patent or trademark.

To secure equal distribution the radio-active compress is packed in the pad in six compartments. When finished, the compress is sterilized by dry heat and packed in sterilized parchment paper.

The amount of radium can be determined by opening the compress and dissolving the contents, by the "Emanation Method" as described in Rutherford's "Radioactive Substances and their Relations," Cambridge, 1913, p. 657.

**STANDARD RADIUM EARTH.**—A mixture consisting chiefly of silica with small quantities of carnotite, 450 Gm. (one pound) containing 0.45 micrograms of radium in the form of radium sulphate and in radioactive equilibrium with its decay products.

*Actions and Uses.*—See Radium.

*Dosage.*—See Radium. For use Standard radium earth is mixed with water and heated for thirty to forty minutes to 100 C.

Manufactured by the Standard Chemical Co., Pittsburgh (The Radium Chemical Co., Pittsburgh). No U. S. patent or trademark.

Standard radium earth is a by-product in the manufacture of radium.

It is a very fine impalpable, brownish-gray powder yielding a thick paste with water.

The amount of radium can be determined by dissolving the Standard radium earth, by the "Emanation Method" as described in Rutherford's "Radioactive Substances and their Radiations," Cambridge, 1913, p. 657.

**STANDARD RADIUM SOLUTION FOR BATHING.**—A 5.2 per cent. barium chloride solution containing radium chloride equivalent to 4.2 micrograms (0.0042 milligrams) of radium element per bottle of 200 Cc. colored with fluorescein.

*Actions and Uses.*—See Radium. The barium in the Standard radium solution for bathing is said to have no effect, the radium chloride and the radium emanation being the only essential ingredients.

*Dosage.*—See Radium. Each 200 Cc., contents of one bottle, contains 4.2 microcuries (11,300 Mache units). When added to a bath containing 150 liters (40 gallons) the concentration of radium emanation in the bath will be about 70 Mache units per liter of bath water.

It is recommended that the patient, after entering a bath at about 90 degrees F., remove the stopper from the bottle of Standard radium solution for bathing and pour out the con-

tents, holding the neck of the bottle just above the surface of the water in the tub to avoid loss of radium emanation. It is advised that the patient remain in the bath at least twenty minutes or, if possible, thirty minutes, and afterward remain in the bath room an hour if possible, the room being kept tightly closed.

Manufactured by the Standard Chemical Co., Pittsburgh (The Radium Chemical Co., Pittsburgh). No U. S. patent or trademark.

The solution is made up by dissolving barium chloride containing suitable amounts of radium in distilled water and then adding  $\frac{1}{60}$  Cc. of a 5 per cent. solution of fluorescein.

The amount of radium may be determined by the "Emanation Method" of Rutherford and Boltwood as described in Rutherford's "Radioactive Substances and their Relations," Cambridge, 1913, p. 659.

#### STANDARD RADIUM SOLUTION FOR DRINKING.—

An aqueous solution of radium chloride, containing barium chloride.

*Actions and Uses.*—See Radium. In view of the small barium content it is claimed that the physiologic action of barium may be ignored.

*Dosage.*—See Radium. The manufacturers recommend that a quantity of Standard radium solution for drinking containing from 2 to 6 micrograms of radium should be taken daily, during or after meals.

Manufactured by the Standard Chemical Co., Pittsburgh (The Radium Chemical Co., Pittsburgh). No U. S. patent or trademark.

*Standard Radium Solution for Drinking (1 microgram Ra).*—A solution containing radium chloride equivalent to 1 microgram of radium (Ra) and 1.3 mg. of barium chloride per bottle of 60 Cc.

*Standard Radium Solution for Drinking (2 microgram Ra).*—A solution containing radium chloride equivalent to 2 micrograms of radium (Ra) and 1.3 mg. barium chloride per bottle of 60 Cc.

One gram of crystallized barium chloride is added to 40 liters of distilled water and the solution allowed to stand for a day; then 1,600 micrograms of radium element in the form of a solution of 60 per cent. pure radium chloride is added, together with 40 Cc. of normal hydrochloric acid. This solution, after analysis by the emanation method to confirm its radium content, is then delivered into the bottles by means of an automatic pipet delivering 50 Cc. of the solution, which contains, as stated, 1.3 mg. of barium chloride and 2 micrograms of radium element. The bottles are then filled almost full to the stopper with distilled water.

The amount of radium may be determined by the "Emanation Method" of Rutherford and Boltwood as described in Rutherford's "Radioactive Substances and their Radiations," Cambridge, 1913, p. 659.

### RESORCIN COMPOUNDS

**EURESOL.**—Resorcin Monacetate.—Resorcinyll Acetate.— $\text{CH}_3\text{CO.O.}(\text{C}_6\text{H}_4\text{OH})$ .—The acetic acid ester of resorcinol,  $\text{C}_6\text{H}_3(\text{OH})_2$ , 1:4.

*Actions and Uses.*—Its action is similar to that of resorcinol, but milder and more lasting because of the gradual liberation of the phenol.

Euresol is said to be useful in acne, sycosis, chilblains, and particularly in the treatment of alopecia and seborrhea.

*Dosage.*—It is applied in from 5 to 20 per cent. ointments and in acetone solution. For scalp lotions 3 to 5 per cent. alcoholic solutions are used.

E. Bilhuber, New York, distributor. German patent Nos. 103,857 and 122,145. U. S. trademark No. 88,894.

*Euresol pro Capillis.*—Euresol perfumed to render it suitable for scalp lotions.

Euresol is obtained by acting on resorcinol with acetic anhydride or acetyl chloride,  $C_6H_4(OH)_2 + CH_3COCl = C_6H_4(OH)COO(CH_3) + HCl$ , or by otherwise replacing one hydroxyl group in resorcinol with an acetyl group.

It is a thick, honey-yellow, oily liquid, boiling at 283 C. and soluble in acetone.

## SALICYLIC ACID COMPOUNDS

To avoid the disagreeable taste and gastric symptoms of salicylates, esters and similar compounds have been introduced, which are more or less insoluble, so that the salicyl radical is liberated only in the intestine or after absorption into the blood. These compounds have little or no direct action on the stomach. Notwithstanding this, nausea and vomiting are frequently induced (Hanzlik, 1913; MacLachlan, 1913), probably owing to action on the central nervous system. In practice these compounds are not superior to sodium salicylate, which does not produce direct gastric irritation when properly guarded by a bicarbonate.

The taste of these compounds is much less objectionable than that of the simpler salicylate salts, but this advantage scarcely balances their high cost.

The alkyl esters (methyl salicylate type) are absorbed readily from the skin and are therefore better for external use than simpler salicylates.

The acyl derivatives (acetylsalicylic acid type) possess a higher analgesic and antipyretic action and have therefore a special field.

The salols contain active phenols which adapt them to intestinal antisepsis.

Salicylic acid compounds may be arranged under four types:

1. Compounds formed by replacing the hydrogen (H) of the hydroxyl group (OH) in salicylic acid, by acyl radicals. To this type, belongs acetyl salicylic acid (aspirin)  $C_6H_4O.(COCH_3).COOH$ .

2. Compounds formed by replacing the hydrogen (H) of the carboxyl group (COOH) in salicylic acid by alkyl radicals: methyl salicylate,  $C_6H_4.OH.COO(CH_3)$ ; and the corresponding ethyl salicylate; methoxymethyl salicylate (meso-

tan); monoglycol salicylate (spirosal); and methyl benzoyl salicylate (benzosalin). Of these benzosalin, ethyl salicylate, mesotan and spirosal are described in N. N. R.

3. Compounds formed by replacing the hydrogen (H) of the carboxyl group (COOH) in salicylic acid by phenol radicals: phenyl salicylate (salol),  $C_6H_4.OH.COOC_6H_5$ ; and the corresponding betanaphthyl salicylate; and acetparamidophenyl salicylate (salophen). Of these, betanaphthyl salicylate and salophen are described in N. N. R.

4. Salicylic compounds in which the salicylic action is subordinate. Those described in N. N. R. are: salipyrine; mercuric salicylate; phenocoll salicylate and santyl.

SALICYL IN VARIOUS DERIVATIVES, IN TERMS OF SALICYLIC ACID AND SODIUM SALICYLATE

100 parts of sodium salicylate = 85.6 parts of salicylic acid = 100 of sodium salicylate.

100 parts of methyl salicylate = 90.7 parts of salicylic acid = 106 of sodium salicylate.

100 parts of acetylsalicylic acid = 77 parts of salicylic acid = 89 of sodium salicylate.

100 parts of salicyl-salicylate = 106.2 parts of salicylic acid = 124 of sodium salicylate.

### Acid Derivatives of Salicylic Acid (Acetylsalicylic Acid Type)

These are employed in rheumatic conditions, and especially as analgesics and antipyretics in colds, neuralgias, etc. Their analgesic effects surpass those of sodium salicylate, with less danger of local irritation. The promiscuous use of acetylsalicylic acid (aspirin) by the laity, especially for the relief of headache, has frequently led to cases of rather severe poisoning, the chief symptoms being edema of the lips, tongue, eyelids, nose or of the entire face; also urticarial rashes, vertigo, nausea and sometimes cyanosis. Some persons are especially susceptible to acetylsalicylic acid and these symptoms are usually ascribed to an idiosyncrasy.

**ACETYSALICYLIC ACID.**—*Acidum Acetylsalicylicum.*—*Acidum Acetylosalicylicum.*—*Aspirin.*— $C_6H_4.O(CH_2CO).COOH$ , 1:2.—The acetyl derivative of salicylic acid.

*Dosage.*—From 0.3 to 1 Gm. (5 to 15 grains), repeated once in three hours until symptoms of salicylism (ringing in the ears, etc.) are noted. It may be administered in the form of a powder, wafers, or capsules. If prescribed as a powder, this may be administered by dissolving it in sweetened water, or by placing it on the tongue followed by a swallow of water. The powder should be dispensed in wax paper.

Acetylsalicylic acid may be obtained by the condensation of acetyl chloride or acetic anhydride with salicylic acid, and subsequent purification by recrystallization from chloroform or other suitable solvent.



It occurs in small colorless crystals or as a white crystalline powder; odorless; of acid taste and reaction; melting point between 128 and 133 C. It is sparingly soluble in cold water, gradually decomposing into acetic and salicylic acids; rapidly decomposed by boiling water; freely soluble in alcohol, soluble in chloroform and ether; also soluble, with decomposition, in solutions of alkali hydroxides and carbonates.

When 0.5 Gm. of acetylsalicylic acid is treated with 10 Cc. of warm sodium carbonate solution (10 Gm.  $\text{Na}_2\text{CO}_3 + \text{H}_2\text{O}$  in 100 Cc.) a clear solution results.

When 0.5 Gm. of acetylsalicylic acid is boiled for from two to three minutes with 10 Cc. of 5 per cent. sodium hydroxide solution, and to the cooled solution 10 Cc. of diluted sulphuric acid are added, a crystalline precipitate is produced, which, after washing and drying, responds to tests for salicylic acid, and the filtrate has the odor of acetic acid.

If to a solution of 0.1 Gm. of acetylsalicylic acid in 1 Cc. of alcohol 48 Cc. of water be added and then 1 Cc. of diluted ferric chloride solution (1 volume of ferric chloride test solution to 100 volumes of water) no greater violet coloration should be produced within two minutes than is produced in a parallel test using 1 Cc. of a standard solution (0.116 Gm. sodium salicylate in 1 liter) in place of the acetylsalicylic acid (limit of *salicylic acid*).

When 0.5 Gm. is shaken with 25 Cc. of distilled water for five minutes and filtered, 5 Cc. portions are not affected by hydrogen sulphide (*heavy metals*), nor with silver nitrate solution (*chloride*), nor with barium chloride solution (*sulphate*).

When heated on platinum, 0.5 Gm. should leave no weighable residue.

It should be kept in well-stoppered containers.

**Acetylsalicylic Acid-M. C. W.**—A nonproprietary brand complying with the standards for acetylsalicylic acid.

Mallinckrodt Chemical Works, St. Louis, Mo.

**Acetylsalicylic Acid-Merck.**—A nonproprietary brand complying with the standards for acetylsalicylic acid.

Merck & Co., New York, distributors.

**Acetylsalicylic Acid-Milliken.**—A nonproprietary brand complying with the standards for acetylsalicylic acid. Sold only in the form of capsules and tablets (see below).

*Acetylsalicylic Acid-Milliken Capsules, 5 Gr.*—Each capsule contains acetylsalicylic acid-Milliken 5 grains.

*Acetylsalicylic Acid-Milliken Tablets, 5 Gr.*—Each tablet contains acetylsalicylic acid-Milliken 5 grains.

Manufactured by Jno. T. Milliken & Co., St. Louis.

**Acetylsalicylic Acid (Aspirin), Monsanto.**—A nonproprietary brand complying with the standards for acetylsalicylic acid.

Manufactured by Monsanto Chemical Works, St. Louis.

**Acetylsalicylic Acid, P. W. R.**—A nonproprietary brand complying with the standards for acetylsalicylic acid.

Manufactured by Powers-Weightman-Rosengarten Co., Philadelphia.

**Acetylsalicylic Acid-Squibb.**—A nonproprietary brand complying with the standards for acetylsalicylic acid.

Manufactured by E. R. Squibb and Sons, New York City.

**Aspirin-L. & F.**—A nonproprietary brand complying with the standards for acetylsalicylic acid.

Manufactured by Lehn and Fink, New York City.

### Alkyl Derivatives of Salicylic Acid (Methyl-Salicylate Type)

These act somewhat more slowly, but otherwise as efficiently as sodium salicylate. They are for the most part saponified in the intestines, but some may be absorbed unchanged. They avoid the disagreeable taste, but frequently cause somewhat more local irritation. They are also quite well absorbed from the skin, and may, therefore, be applied externally, usually dissolved in olive oil. Methyl salicylate is official in the U. S. Pharmacopeia. See under Methylis Salicylas.

**BENZOSALIN.**—Methylis Benzoyl-Salicylas.—Benzoyl-Salicylic-Acid-Methylester.—Methyl Benzoyl-Salicylate.— $C_6H_5O(CH_3).CO.O.(C_6H_5CO)$ , 1:2.—The benzoyl salicylic acid ester of methyl alcohol.

**Actions.**—Benzosalin is decomposed in the intestines, into its constituents, benzoic and salicylic acids.

**Dosage.**—From 0.5 to 1 Gm. ( $7\frac{1}{2}$  to 15 grains). Daily dose 3 to 4 Gm. (45 to 60 grains) in powder or tablets.

Manufactured by F. Hoffmann-La Roche & Co., Basle, Switzerland (The Hoffmann-La Roche Chemical Works, New York). U. S. patent No. 799,706 (Sept. 19, 1905; expires 1922). U. S. trademark No. 58,757.

**Benzosalin Tablets, 5 grains.**—Each tablet contains benzosalin 0.3 Gm. (5 grains).

Benzosalin is prepared by a reaction between the methyl ester of salicylic acid and benzoyl chloride in the presence of sodium hydroxide. The resulting product is washed with water and after drying is crystallized out from alcohol.

Benzosalin consists of fine, white crystals with a very faint aromatic odor. It melts at about 85 C. It burns leaving no residue. It dissolves readily in chloroform, benzene and in 35 parts of 90 per cent. cold alcohol, also in pure, concentrated sulphuric acid.

**ETHYL SALICYLATE** — Æthylis Salicylas.— $C_6H_5.OH.C.O.O.(C_2H_5)$ .—The salicylic acid ester of ethyl alcohol analogous to methyl salicylate (oil of wintergreen).

**Actions and Uses.**—Ethyl salicylate has the same action as methyl salicylate, but is said to be less irritant and less toxic.

**Dosage.**—From 3 to 6 Cc. (5 to 10 minims) three or four times a day.

Ethyl salicylate is made by the action of salicylic acid on ethyl alcohol in the presence of sulphuric acid and subsequent purification.

It is a transparent, colorless, volatile liquid, possessing a pleasant characteristic odor and taste. Its specific gravity is 1.132 at 20 C. and it boils at 230-232 C. It is insoluble in water, but soluble in alcohol.

**Ethyl Salicylate-Merck.**—A nonproprietary brand complying with the standards for ethyl salicylate.

Merck & Co., New York, distributors.

**Sal-Ethyl.**—A proprietary name applied to ethyl salicylate.

Manufactured by Parke, Davis & Co., Detroit. U. S. trademark.

*Sal-Ethyl Globules.*—Each globule contains sal-ethyl 0.33 Cc. (5 minims).

**MESOTAN.** — Ericin. —  $C_6H_4.OH.CO.O(CH_2.O.CH_3)$ . — Methyl-oxyethyl salicylate, an ester of salicylic acid, analogous to methyl salicylate.

*Actions and Uses.*—The action of mesotan is similar to that of oil of wintergreen, but is more irritating to the skin.

*Dosage.*—Being quite irritating when applied pure to the sensitive skin, it is employed diluted with an equal volume of olive oil, and without friction. Simple application to the affected part (which need not be covered, or, if so, only slightly) is said to give prompt relief.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent No. 706,018 (Aug. 5, 1902; expires 1919). U. S. trademark No. 39,017.

Mesotan is prepared by the action of chlormethyl ether on salicylates thus:  $C_6H_4.OH.COONa + CH_2Cl.O.CH_3 = NaCl + C_6H_4.OH.COO(CH_2.O.CH_3)$ .

It is a clear, yellowish, faintly aromatic, oily fluid, specific gravity 1.2 at 15 C. and boiling at about 162 C. It is with difficulty soluble in water, but readily soluble in the usual organic solvents and miscible with oils in all proportions. Above 100 C. it is decomposed, yielding salicylic acid, formaldehyde and methyl alcohol, and it is likewise decomposed to a certain extent by moisture in the air.

Its watery solution gives a violet color with ferric chloride and after heating or exposure to moisture it responds to the usual tests for formaldehyde. Concentrated sulphuric acid colors it red.

It should be kept in a cool place and preserved dry in well-stoppered bottles.

**SPIROSAL.** — Monoglycol-Salicylate. —  $C_6H_4.OH.CO.O.(CH_2.CH_2.OH)$ .—The salicylic acid ester of monoglycol.

*Actions and Uses.*—When spirosal is applied to the skin about one-fifth to one-sixth of the amount used is absorbed; usually it causes very little irritation even when rubbed in thoroughly.

*Dosage.*—It is used undiluted or mixed with from 2 to 3 parts of alcohol or in a mixture with olive oil, 1 to 8, or in ointments with equal parts by weight of petroleum or lard.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent No. 794,982 (July 18, 1905; expires 1922). U. S. trademark No. 62,856.

Spirosal is prepared by the action of ethyleneglycol on salicylic acid.

It is an almost odorless and colorless oily fluid, with a boiling-point of from 169 to 170 C. at 12 mm. pressure. It is easily soluble in alcohol, ether, chloroform and benzol and soluble in about 110 parts of water and 8 parts of olive oil.

Tests: 0.5 Gm. spirosal is saponified with 5 Cc. soda lye by slight warming, the clear fluid diluted with water and acidified with dilute sulphuric acid; fine crystalline needles of salicylic acid are formed, which, after being extracted with ether and the latter then evaporated, can be identified by the melting point and ferric chloride reaction. The saturated aqueous solution obtained by shaking 1 Cc. spirosal with 50 Cc. of water gives a filtrate, which becomes intensely violet on addition of ferric chloride, but should not be changed by barium nitrate or silver nitrate; 0.5 Gm. of spirosal when added to 2 Cc. of concentrated sulphuric acid should give a light yellow and not a brownish color; 0.3 Gm., if incinerated on platinum foil, should not leave any weighable residue.

### Phenol Derivatives of Salicylic Acid (Salol Type)

Phenol derivatives of salicylic acid of the salol type are used mainly as intestinal antiseptics. Phenyl salicylate (salol) is official.

**MERCURIC SALICYLATE.**—See Mercuric Compounds. Inorganic.

**PHENOCOLL SALICYLATE.**—See Phenocoll Compounds.

**SANTYL.**—See Sandalwood Oil Derivatives.

**BETANAPHTHYL SALICYLATE.**—See Naphthol Compounds.

**SALOPHEN.**—See Phenetidin Derivatives.

### Salicylic Compounds in which the Salicylate Action is Subordinate

**SALIPYRIN.**—See Pyrazolon Derivatives.



## SANDALWOOD OIL DERIVATIVES

The oil of sandalwood is eliminated chiefly by the kidneys and is a fairly effective urinary antiseptic, although it is inferior to hexamethylenamine in acid urines. (Jordan: *Biochem. Jour.* 5:2741, 1911.) It is used particularly in subacute or chronic urethritis and cystitis. The oil at times is disturbing to the stomach and medicinal doses may cause irritation of the bladder with dysuria and pain in the kidney region and urethra.

The advantage claimed for the new derivatives of santal oil is that they are less irritating than the oil itself.

**ARHEOL.**—Santalol.— $C_{15}H_{26}O$ .—A sesquiterpenic alcohol, the chief constituent of sandalwood.

*Actions and Uses.*—The action of arheol is the same as that of sandalwood oil. It is claimed that because of its purity it does not occasion disturbance of the stomach or the kidney. It is used in urethritis, cystitis and vesical catarrh, especially from gonorrhea.

*Dosage.*—0.4 to 0.6 Gm. (6 to 9 grains). Arheol is marketed only in capsules containing 0.20 Gm. (3 grains) of which 9 to 12 capsules are to be taken daily.

Manufactured by Placide Alexandre Astier, Paris, France (E. Fougera & Co., Inc., New York). No U. S. patent. U. S. trademark No. 72,513.

*Arheol Capsules.*—Each capsule contains arheol 0.2 Gm. (3 grains).

Arheol is a colorless, oily liquid; specific gravity, 0.979 at 15 C. It is insoluble in water but soluble in alcohol. It boils under 11 mm. pressure at 169 C., and under ordinary pressure at about 300 C.

**CARBOSANT.**—Santalolis Carbonas.—Santalyl Carbonate— $(C_{15}H_{23}).O.CO.O.(C_{15}H_{23})$ .—The carbonic acid ester of santalol.

*Actions and Uses.*—The action of carbosant, which is chemically broken up into its component parts in the intestine, is identical with that of santalol, the active constituent of official sandalwood oil.

*Dosage.*—0.6 Cc. (10 minims) three times daily. It may be given in capsules, each containing 0.3 Gm. (5 grains), 2 capsules being given three times daily.

Manufactured by the Chemische Fabrik von Heyden at Radebeul near Dresden, Germany (Heyden Chemical Works, New York). German patent No. 182,627. No U. S. patent. U. S. trademark applied for.

Carbosant is produced by the chemical interaction of santalol with carbonyl chloride,  $COCl_2$ , and alkalis, or with carbonic acid esters.

Carbosant is an oily yellow fluid, almost tasteless and odorless, insoluble in water, and soluble in alcohol and ether. It contains 94 per cent. of santalol.

Carbosant is saponified when heated with an alcoholic solution of caustic alkali with the production of potassium carbonate and santalol, both of which can be identified by appropriate tests.

**SANTYL.**—Santalolis Salicylas.—Salicylic Ester of Santalol.—Santalyl Salicylate.— $C_9H_7OH.COO(C_{15}H_{25})$ .—The salicylic acid ester of santalol.

*Actions and Uses.*—It is said that santyl passes the stomach unchanged, but is slowly split up in the intestines into its constituents, santalol and salicylic acid. Santyl is claimed to have the same actions as sandalwood oil, except that because of the slow liberation of santalol, it produces less irritation of the gastro-intestinal tract or of the kidneys and urinary passages, and no unpleasant odor or eructations.

It is claimed to be useful like santal oil for gonorrheal urethritis.

*Dosage.*—1.5 Cc. (24 minims) usually given in 3 capsules of 0.5 Cc. (8 minims) each, three times a day.

E. Bilhuber, New York, distributor. German patent No. 173,240. U. S. patent No. 862,858 (Aug. 6, 1907; expires 1924). U. S. trademark No. 61,255.

According to the German patent the neutral esters of sandalwood oil are produced by heating the oil with the respective acid anhydrides and subsequent purification of the product.

Santyl is a yellowish oil with only a faint balsamic odor and taste; specific gravity, 1.07 at 15 C.; it boils under 20 mm. pressure at 121 C. to 126.6 C. with partial decomposition. It is insoluble in water, but soluble in about 10 parts of alcohol.

It is incompatible with alkalies and with the usual incompatibles of sandalwood oil and of salicylates.

Santyl should possess the physical constants given above. On saponification with alcoholic sodium hydroxide it should yield approximately 40 per cent. of salicylic acid and 60 per cent. of santalol.

**SCARLET R MEDICINAL BIEBRICH.**—Rubrum Scarlatinum. — Toluy-Azo-Betanaphthol. —  $CH_3C_6H_4N:N C_6H_5$ .  $(CH_3)N:N.C_{10}H_7.OH$ .—A compound of betanaphthol and diazotised amido-azo-ortho-toluol.

*Actions and Uses.*—Biebrich scarlet R medicinal has a marked power of stimulating the proliferation of epithelial cells.

Opinions are divided as to its clinical value, but it is used to promote the growth of epithelium in the treatment of burns, wounds, chronic ulcers, etc. In chronic ulcers, however, it is requisite that the local circulation be good in order to obtain a permanent result.

*Dosage.*—This preparation is generally used in the form of an ointment containing from 4 to 8 per cent. of the substance. The 8 per cent. ointment is somewhat irritating and should be alternated with a soothing ointment.

Biebrich scarlet R medicinal is a dark brownish red powder, nearly insoluble in water, slightly soluble in benzene and acetone and easily soluble in chloroform, oils, fats and phenols. It is slightly soluble in cold alcohol, somewhat more soluble in hot alcohol, while warm petrolatum and paraffin dissolve rather large quantities. When heated to 175 C. it softens, begins to melt at from 181 to 188 C. and at 260 C. swells up and decomposes. Further heating yields heavy brown, aromatic vapors, which burn, leaving a difficultly but completely combustible residue. The saturated aqueous solution is a clear scarlet red color, which on dilution or in thin layers has a bluish tinge. It is decomposed by nitric acid.

If about 1 Mg. of Biebrich scarlet R medicinal be sprinkled on about 1 Cc. concentrated sulphuric acid it will dissolve in the acid with a bluish-green color, which, on diluting with water, changes consecutively to blue, then to purple and finally to red. After a time a brown flocculent precipitate gradually forms. If to a small quantity of Biebrich scarlet R medicinal a few Cc. of alcohol and 2 drops of concentrated hydrochloric acid be added and the mixture boiled the solution will take on a purple color. This solution on the addition of a few drops of glacial acetic acid becomes scarlet red. If not too small a quantity of the substance was taken it will crystallize out of the acetic acid solution in the form of fine needles. If about 0.5 Gm. Biebrich scarlet R medicinal be heated to boiling with  $\frac{3}{4}$  Cc. acetic acid and then, while boiling, zinc dust be added, the solution will become colorless. A bluish color appears on exposure of this solution to air.

**Scarlet R Medicinal-Kalle.**—A nonproprietary brand complying with the standards for scarlet R medicinal Biebrich.

Manufactured by Kalle & Co., Aktiengesellschaft, Biebrich a/Rh., Germany (Heilkraft Medical Co., Boston). No U. S. patent or trademark. Sold in the form of ointment only.

**Scarlet R Salve.**—Scarlet R Salve is a mixture containing Biebrich scarlet R medicinal-Kalle & Co., 8 parts, eucalyptol 2 parts and petrolatum 90 parts.

Prepared by the Heilkraft Medical Company, Boston.

**Scarlet R Medicinal Biebrich-Merck.**—A nonproprietary brand complying with the standards for scarlet R medicinal Biebrich.

Merck & Co., New York, distributors.

## SCOPOLAMINE

The scopolamine (or hyoscine) of the U. S. P. consists of the levorotatory compound. The optically inactive compound has the same effect on the central nervous system as has the official or levorotatory compound; it has but one-half the activity on peripheral organs (eye, heart, secreting glands). The absence of the latter action may in some cases be desirable, and in such cases there may be advantages in using the optically inactive compound; this has been introduced under the name "euscopol."

**EUSCOPOL.**—Optically Inactive Scopolamine Hydrobromide.— $C_{17}H_{21}NO_4.HBr$ .—The optically inactive hydrobromide of scopolamine.

*Actions and Uses.*—It is employed as a substitute for the official scopolamine hydrobromide. It has the same effect on the central nervous system as has the official preparation but is less active than the latter in checking secretions, dilating the pupil, etc.

*Dosage.*—0.0003 Gm. ( $\frac{1}{200}$  grain).

Manufactured by J. D. Riedel, Aktiengesellschaft, Berlin, Germany (Riedel & Co., New York). German trademark. No U. S. patent. U. S. trademark No. 88,640.

Euscopol is obtained from ordinary optically active scopolamine by treatment with a weak alcoholic solution of potassium hydroxide, subsequent purification of the resulting optically inactive base from which the hydrobromide (euscopol) is prepared.

Euscopol occurs as colorless crystals, easily soluble in water and alcohol, but slightly soluble in ether and chloroform. It melts at 181 to 185 C. The solution is optically inactive.

Excepting the optical inactivity and the difference in melting points, euscopol responds in general to the tests for the official scopolamine hydrobromide. The picrate of the optically active preparation crystallizes in thin needles, melting at 190 to 191 C., while euscopol picrate crystallizes in long indented tablets, which melt at 192 to 194 C. The picrate is prepared by adding 10 Cc. of a saturated aqueous solution of picric acid to a solution of 0.1 Gm. euscopol in 4 Cc. water. The resulting emulsion is dissolved by warming and the solution allowed to stand, whereupon crystals of the picrate gradually form.

If 0.1 Gm. euscopol be dissolved in 5 Cc. water and treated with 5 drops of a 1:1,000 potassium permanganate solution, the violet color should still be visible after five minutes (*apoptropin*).

**SCOPOLAMINE STABLE-ROCHE.**—Scopomannit.—An aqueous solution of pure scopolamine hydrobromide, protected against decomposition by the addition of 10 per cent. of mannite, supplied in ampules, each containing 1.2 Cc. (1 Cc. contains 0.0003 Gm. scopolamine hydrobromide).

*Actions, Uses and Dosage.*—The same as those of Scopolamine hydrobromide, U. S. P. (See Useful Drugs.)

Manufactured by F. Hoffmann-LaRoche and Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York). No U. S. patent. German patent No. 266,415. U. S. trademark Nos. 103,288 and 103,289.

Scopolamine stable-Roche is prepared from freshly manufactured scopolamine hydrobromide having an optical activity of  $-26.0^\circ$  for the sodium line (determined in an aqueous solution containing the equivalent of 4.5 Gm. of anhydrous scopolamine hydrobromide in 100 Cc. at a temperature of 15 C. in a 100 millimeter tube) and a melting point of 195 C. by dissolving in an aqueous 10 per cent. solution of mannite.



That scopolamine stable-Roche contains all of its scopolamine in an undecomposed state may be determined by comparing its action with that of a freshly prepared solution of scopolamine hydrobromide. For this purpose the manufacturers recommend the method of Langer, in which the frog heart is stopped by muscarine, or, better, by pilocarpine, and the systolic beat is reestablished by the addition of scopolamine, which is antagonistic to both muscarine and pilocarpine.

## SERUMS AND VACCINES

Under this heading are described in the following pages agents of a complex biologic nature which are used in the treatment and diagnosis of disease and which depend for their action on various phases and relations of immunity.

*Federal Regulation.*—The urgent need for control of many of these potent and, in some cases, dangerous products has been partly met by a federal law entitled "An act to regulate the sale of viruses, serums, toxins, and analogous products in the District of Columbia, to regulate interstate traffic in said articles and for other purposes." Under this law the interstate sale of these products is expressly forbidden unless the manufacturer holds a license from the Secretary of the Treasury. To obtain such a license, application must be made to the Surgeon-General of the Public Health Service, who thereupon designates an officer of that service to make a careful examination of the stables, laboratory facilities, materials, methods, personnel, animals, and thoroughness of testing.

Samples are obtained, some from the open market and others from the manufacturer, and are examined from time to time in the Hygienic Laboratory of the Public Health Service. Furthermore, any health officer or physician is at liberty to submit samples to the Hygienic Laboratory and request examination of them.

Licenses are revokable at any time and are issued for only one year, necessitating thorough inspection and examination of samples at least yearly.

In general, products are examined for bacteriologic purity, freedom from excess of preservative, and for potency, if a potency test is applicable. Definite legal potency standards exist for only two products—diphtheria antitoxin and tetanus antitoxin; for antityphoid vaccine, antimentingococcus serum, antipneumococcus serum, and antidysenteric serum, tentative potency standards have been established; for others, no control of the assumed value is practicable.

The regulations and practices change from time to time and manufacturers are required to keep abreast of the best technic and progress. On each package must be plainly stated the name of the product, the name of the establishment, license number, date beyond which the product cannot be expected to yield its full potency or date of manufacture or issue with a statement of the period of probable potency, and

a laboratory serial number. It would be well if in the use of these products, records were habitually made by the physician of the serial numbers which identify the particular lot, since such record would be useful for comparing efficiencies.

It is to be noted that the protection of the federal law is of avail only in the case of prophylactic and therapeutic preparations which are shipped for interstate sale. Only products which are licensed for interstate sale and which have not been found to conflict with the rules of the Council will be found listed here. In purchasing the products for use, preference should be given to those which have been kept continually at a low temperature.

*The Council's Rule for Dating.*—The practice now followed by manufacturers (in accordance with the federal law) of placing on the containers of biologic products the date beyond which these agents are not to be regarded as dependable, has not been uniformly satisfactory.

For diphtheria and tetanus antitoxins there are definite official potency standards readily determinable by dependable tests. Consequently the dates on packages of these antitoxins mean that the manufacturer vouches for their potency up to the time indicated, assuming that they have been kept under proper conditions. There are no methods, however, for determining the potency of the great majority of serums and vaccines, particularly the bacterial vaccines. Moreover, while we do not know the exact effect of age on these substances, there is sufficient reason for preferring a fresh product to one of uncertain age.

Probably the most important factor in the preservation of such potency as these agents possess is the temperature at which they are kept; low temperatures, such as are obtained in cold storage, favor conservation, while ordinary room temperatures contribute to deterioration of their specific properties. Manufacturers, generally, are careful about the proper keeping of biologic products while in their hands; but they have no control over the preparations after they are placed on the market, though a commendable effort is made on the part of some manufacturers to follow up and safeguard their preparations.

That the physician may know the age of a given product when it reaches him, and that he may be in position to judge whether it has been kept unduly long under conditions which are deemed unfavorable, the Council on Pharmacy and Chemistry has adopted a rule that, after Dec. 31, 1919, to be accepted for, or retained in, New and Nonofficial Remedies, biologic products must bear on each trade package the date of the manufacture of the particular preparation.

Since there is no potency standard for biologic products other than for diphtheria and tetanus antitoxins, the term "date of manufacture," or, at the pleasure of the individual

manufacturer, "date of issue," "manufactured" or "issued," shall be acceptable in accordance with these conditions:

1. For products for which an efficient potency standard exists, the date of testing shall be taken as the date of manufacture. For vaccine virus date of satisfactory potency test shall be taken.

2. For other products of animal origin, the date of removal from the animals (e. g., bleeding, in case of serums) shall be taken as the date of manufacture.

3. For products of bacterial origin, the date of the killing of the bacteria shall be taken as the date of manufacture. "Date of issue" or "issued" may be used:

4. When adequate cold storage facilities are available to indicate date of removal from cold storage in accordance with the following: Product may be kept for not to exceed one year at or below  $+5^{\circ}\text{C}$ . or for not to exceed six months at or below  $+8^{\circ}\text{C}$ ., or for not to exceed three months at or below  $+15^{\circ}\text{C}$ . This section does not apply to living viruses excepting that vaccine virus may be stored at or below  $+5^{\circ}\text{C}$ . for not to exceed three months, and at or below  $0^{\circ}\text{C}$ . for one year.

*Added Preservatives.*—The preservation of serums, vaccines, etc., requires the addition of some preservative. Although some objections have been raised to this practice it is generally agreed that the use of an antiseptic is an additional safeguard to prevent contamination during the later manipulations of the product, and the small amount of antiseptic added has practically no deleterious effects. In the preservation of serums which are used in larger volumes, the amount and character of the preservative is a more important matter.

Liquor cresolis compositus was formerly used as a preservative, but its use has been abandoned. Phenol is used by some manufacturers in a strength of from 0.25 to 0.5 per cent. The most commonly used antiseptic is cresol U. S. P. or trikresol N. N. R. in from 0.2 to 0.4 per cent.

*Immunity Reactions.*—Immunity, in its broadest medical sense, means resistance to disease or harm. To attempt a more precise definition would give emphasis to certain theories or parts of the subject to the exclusion of others. The science of immunity, however, is chiefly concerned with the specific reactions which occur after the micro-organisms of an infectious disease or a complex substance similar to the products of micro-organisms is introduced within the body. In general, these reactions are specific; for instance, diphtheria toxin stimulates the body to produce an antitoxin which combines with no other toxin save that produced by the diphtheria bacillus.

The reactions of immunity may act either to prevent disease or to cure it, or to distinguish one disease from another.

Accordingly, the products enumerated in this section may be used in prophylaxis, in treatment, or in diagnosis. Immunity may be natural to the individual or it may be acquired. That which is called into play by the use of these products is of course acquired immunity, and artificial at that, i. e., not conferred by a casual attack of the disease in question.

There is a further classification of acquired immunity into passive and active forms. In active immunity the agents which actually perform the protective work are created within the body. In passive immunity these agents are introduced ready formed from without. This gives us a basis for the classification of the therapeutic products. Those of the first class, the serums, and the antitoxins, which are derived from the serums, are intended to produce passive immunity; they are "antibodies," which directly antagonize the invading bacteria and toxins.

The other great class of immunity products are called "antigens" because they are administered in the hope that their presence in the body will stimulate the production of true antibodies similar to those found in the serums.

This active immunity, formed by the introduction of antigens, is in general slower in appearance but more lasting than the passive immunity caused by the introduction of foreign antibodies. It must be remembered also that the antigen is of the same nature as the disease which is to be combated, and that in using antigens we are calling on the cells and fluids of the individual to produce their own protecting substances. To the class of antigens belong the vaccines, viruses, tuberculin, toxins, and bacterial vaccines.

These antigens and antibodies are of unknown chemical composition, of high molecular weight, and even when soluble, are not easily absorbed without change from the gastrointestinal tract. Hence, they must be administered parenterally; that is, by the subcutaneous, intramuscular, intraneural, intraspinal, or intravenous route in order to reach tissues not directly accessible.

### **I.—Antibodies Used for Prophylactic or Therapeutic Purposes**

Antibodies are usually directed against the toxins or soluble products of bacteria or against the bacteria themselves. All the antibodies enumerated below are formed in the blood serum of the larger domestic animals by active immunization; that is, by injecting the animal with an antigen. The animal is then bled to furnish the serum, which may afterward be purified, in the case of the antitoxins, to remove as many inactive substances as possible, leaving the antitoxin in a concentrated form. The crude serum or the purified form may further be dried for more permanent preservation or for more convenient administration in some cases.



**NORMAL HORSE SERUM.**—The serum of normal horse blood obtained in a sterile manner and passed through a Berkefeld filter.

*Actions and Uses.*—Though not a specific immunity product, normal horse serum is classed commonly with the other serums. It is claimed to be used with success in hemorrhagic conditions to increase the coagulability of the blood.

The injection of horse serum is followed in certain individuals by more or less pronounced symptoms of anaphylactic shock. In its mildest form this appears as an urticarial eruption on the skin or an edematous swelling of the mucous membranes. In more severe cases there may be a fall of temperature, increased rapidity of pulse, quickened and difficult respiration, cyanosis, and occasionally convulsions. In rare cases the attack comes on with great suddenness and may terminate fatally. These cases of sudden death occur especially in asthmatics and in patients who are naturally hypersensitive to horse serum. Ordinary serum disease manifests itself by milder but similar symptoms which appear from a few days to one or two weeks after the injection of the serum. In addition to the eruptions which are urticarial or scarlatiniform, joint pains and swelling of the joints sometimes occur.

Atropine hypodermatically is a useful remedy for the severer manifestations of serum poisoning. Most cases of this poisoning have occurred after the use of antitoxic serums, but emphasis should be laid on the fact that these symptoms are not caused by antitoxin, but are due to hypersusceptibility to the proteins of horse serum.

The Cutter Laboratory, Berkeley, Calif.

*Normal Serum (from the Horse).*—Marketed in syringes containing 10 Cc. and in bottles containing 50 Cc.

The Gilliland Laboratories, Ambler, Pa.

*Normal Horse Serum.*—Marketed in syringes each containing 10 Cc.; also in ampules containing from 10 to 100 Cc. as ordered.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Normal Horse Serum.*—Marketed in a special syringe containing 10 Cc., with sterile needle. Also in an aseptic glass vial, containing 100 Cc.

H. K. Muiford Co., Philadelphia.

*Normal Serum (from the Horse).*—Marketed in packages of two syringes, each containing 10 Cc. Also in single vials of 100 Cc. each.

National Vaccine and Antitoxin Institute, Washington, D. C.

*Sterile Normal Horse Serum.*—Marketed in syringes containing respectively 10, 15 and 20 Cc.

E. R. Squibb & Sons, New York.

*Normal Horse Serum.*—Marketed in packages of two syringes, each containing 10 Cc. Also in vials of 20 Cc. each, without a syringe.

#### A.—ANTITOXINS

The antitoxins are among the simplest and most useful of the antibodies. As the name implies, they antagonize toxins. Though toxins may be secreted by plants other than the bacteria and by some animals, e. g., in snake venoms, the typical toxins are the soluble poisons thrown off by diphtheria and tetanus bacilli.

Diphtheria and tetanus are dangerous diseases almost entirely on account of the action of these toxins, and conversely, their prevention or cure, when the organisms have once gained entrance to the body, depends on the work of the particular antitoxin. Though the presence of the toxin stimulates the body to produce antitoxin, this active immunity may not be enough to save life; and, at any rate, assistance by the injection of antitoxin, ready made in the blood serum of another animal, hastens the cure or may prevent the disease.

Antitoxins are relatively simple and relatively stable, as compared with some of the other bodies taking part in the reactions of immunity.

In some cases eruptions occur after injection of antitoxin, rarely swelling and pain in the joints. In other cases more severe symptoms have been observed and in a few instances sudden death has occurred. These conditions are due, not to the antitoxin but to the horse serum in which it is contained. (See Normal Horse Serum.)

#### DIPHTHERIA ANTITOXIN UNCONCENTRATED.—

For description see the U. S. Pharmacopeia under Serum Antidiphthericum.

*Dosage.*—See Useful Drugs.

Burroughs Wellcome & Co., London, England, and New York.

*Diphtheria Antitoxin Serum.*—Serums of different values from a number of horses are mixed to yield a definite value (from 450 to 500 units per Cc.), also a high-potency serum, 1 Cc. of which contains 1,000 units. Trikresol (0.3 per cent.) is added as a preservative. Marketed in hermetically sealed vials containing from 1,000 to 4,000 (Ehrlich-Behring) units; also a high-potency serum containing from 1,000 to 10,000 units.

Cutter Laboratory, Berkeley, Calif.

*Diphtheria Antitoxin.*—Marketed in syringes containing 1,000, 2,000, 3,000, 4,000 and 5,000 units.

Parke, Davis & Co., Detroit.

*Antidiphtheric Serum, U. S. P.*—Preserved with 0.4 per cent. trikresol; marketed in piston syringe containers of from 500 to 5,000 units each.

**DIPHThERIA ANTITOXIN, CONCENTRATED.**—For description see U. S. Pharmacopeia under Serum Antidiphthericum Purificatum.

*Dosage.*—See Useful Drugs.

Cutter Laboratory, Berkeley, Calif.

*Diphtheria Antitoxin Globulin.*—Marketed in syringes containing 1,000, 2,000, 3,000, 4,000, 5,000 and 10,000 units each.

Department of Health, City of New York.

*Refined and Concentrated Diphtheria Antitoxin (Globulin).*—The preparation is a solution of the globulins of the blood which are soluble in a saturated sodium chloride solution; this contains most of the antitoxin. Preserved with chloroform. Marketed in syringes containing from 2,000 to 5,000 units, each Cc. containing 800 to 1,500 units. Also in bulk.

The Gilliland Laboratories, Ambler, Pa.

*Gilliland's Concentrated and Refined Diphtheria Antitoxin.*—Prepared according to Banzhaf's method and preserved with 0.4 per cent. trikresol, contains less than 20 per cent. of solids. Marketed in syringes containing each 1,000, 3,000, 5,000, 7,500, 10,000, 15,000 and 20,000 units.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Diphtheria Antitoxin.*—Only antidiphtheric globulin is sold; this is marketed in syringes containing from 500 to 10,000 units each; also in vials containing from 1,000 to 5,000 units each. The latter are prepared more particularly for the use of Boards of Health.

H. K. Mulford Co., Philadelphia.

*Diphtheria Antitoxin, Concentrated (Globulin).*—Prepared from serum antidiphthericum by the removal, by precipitation at 33⅓ per cent. saturation with ammonium sulphate, of the serum albumins and globulins. The product consists essentially of a soluble serum globulin freed from inorganic salts by dialysis and redissolved in physiologic salt solution. Preserved with not more than 0.25 per cent. trikresol or not more than from 0.1 to 1 per cent. chloroform. Marketed in syringes containing, respectively, 1,000, 2,000, 3,000, 4,000, 5,000, 7,500 and 10,000 units, the first being an emergency dose and the remainder therapeutic doses.

National Vaccine and Antitoxin Institute, Washington, D. C.

*Diphtheria Antitoxin, Concentrated.*—Prepared according to Gibson's method. Preserved with chloroform. Marketed in syringes containing from 500 to 6,000 units.

Parke, Davis & Co., Detroit.

*Antidiphtheric Globulins*.—Marketed in piston syringe containers of from 500 to 5,000 units each.

E. R. Squibb & Sons, New York.

*Purified Diphtheria Antitoxin (Antidiphtheric Globulin)*.—Put up in a syringe container.

*Dosage*.—Immunizing dose, 1,000 units; curative dose, 2,000, 3,000, 4,000, 5,500, 7,500 and 10,000 units.

**DIPHTHERIA ANTITOXIN, DRIED**.—For description see the U. S. Pharmacopeia under Serum Antidiphthericum Siccum.

*Dosage*.—See Useful Drugs.

Parke, Davis & Co., Detroit.

*Antidiphtheric Globulins (dry)*.—Marketed in packages of 3,000 units each. The dry powder is readily soluble in water and will keep indefinitely.

**TETANUS ANTITOXIN, UNCONCENTRATED**.—For description see the U. S. Pharmacopeia under Serum Antitetanicum.

*Dosage*.—See Useful Drugs.

The Cutter Laboratory, Berkeley, Calif.

*Tetanus Antitoxin for Human Use*.—Marketed in syringes containing 1,500, 3,000 and 5,000 units each.

**TETANUS ANTITOXIN, CONCENTRATED**.—For description see the U. S. Pharmacopeia under Serum Antitetanicum Purificatum.

*Dosage*.—See Useful Drugs.

Department of Health, City of New York.

*Antitetanic Globulin*.—Preserved with chloroform. Marketed in vials containing 1,500 to 5,000 units.

The Gilliland Laboratories, Ambler, Pa.

*Gilliland's Concentrated and Refined Tetanus Antitoxin*.—Marketed in syringes containing each 1,500, 3,000 and 5,000 units.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Concentrated Antitoxin (Globulin)*.—Marketed in syringes containing 1,500, 3,000 and 5,000 units each.



H. K. Mulford & Co., Philadelphia.

*Tetanus Antitoxin*.—Marketed in syringes containing 1,500 units (immunizing dose) and 3,000 and 5,000 units (therapeutic dose).

Parke, Davis & Co., Detroit.

*Antitetanic Serum*.—Marketed in piston containers, 1,500 units each, and in bulbs containing 1,500 units each.

E. R. Squibb and Sons, New York.

*Tetanus Antitoxin, Purified*.—Marketed in three packages containing, respectively, 1,500 units (immunizing dose) 3,000 units (curative dose) and 5,000 units (curative dose) put up in syringe containers.

**TETANUS ANTITOXIN, DRIED**.—For description see the U. S. Pharmacopeia under Serum Antitetanicum Siccum.

*Dosage*.—See Useful Drugs.

Parke, Davis & Co., Detroit.

*Dry Antitetanic Serum*.—Marketed in vials each containing the equivalent of 30 Cc. of the liquid.

*Antitetanic Dusting Powder*.—The dried serum mixed with a small quantity of chloretone (chlorbutanol).

#### B.—ANTIBACTERIAL SERUMS

More complex in action than the antitoxins and much less satisfactory for therapeutic purposes are those antibodies which resist the bacteria themselves. This field is open to much controversy, both theoretical and practical; for one thing, in such cases we are attempting to act on living organisms, multiplying at various rates and subject to various changes.

Of the antibacterial substances, the bacteriolysins are those which dissolve bacteria and are considered to be the bactericidal bodies proper. They act only in the presence of complement, a substance which is present in fresh blood serum and which is destroyed by heating. The bacteriolysins themselves withstand moderate heating; that is, they are thermostable, like the simpler antitoxins.

Aside from the direct killing of the bacteria by the blood serum, the invaders may be taken up by the leukocytes—not as a rule, however, until they have been acted on by other substances in the serum, known, respectively, as bacteriotropins and opsonins, according as they resist moderate heat or not. The bacteriotropins are relatively simple, like antitoxins, and are found especially in immune serums; that is, in serums of animals which have been artificially immunized by the injection of antigens, such as the serums in the list below.

The opsonins are present to some extent in normal serums and are made useless by heating. In fact, they may consist of two parts, one part being thermostabile and the other thermolabile (heat-sensitive), the latter being the complement mentioned above as present in all serums.

The amboceptor, which is demonstrated by the technic of complement fixation (to be mentioned later under diagnostic preparations), is considered by some to be distinct from the bacteriolytic amboceptor, and it may be a fourth antibody. A fifth may be anti-endotoxin. Since in the case of these bacteria no large amount of soluble toxin can be demonstrated to be excreted, as is the case with diphtheria and tetanus bacilli, some have thought that their deleterious action is due to poisonous substances, "endotoxins," which are held firmly as part of the bacterial body and are set free only on the disintegration of the latter. It is against these endotoxins that the anti-endotoxins of immune serums are supposed to act.

True toxins have been found with some of these bacteria; and antitoxins have been found in their immune serums. These have no importance comparable with the toxins and antitoxins of diphtheria and tetanus. Other antibodies have also been named, such as anti-aggressins, to neutralize the aggressins to which the virulence of bacteria is assigned by some.

The agglutinins and precipitins are antibodies which act directly without complement, causing the bacteria to gather in clumps or precipitating bacterial extracts.

One consideration which makes antibacterial serum therapy less hopeful than antitoxic therapy is that the concentration of measurable antibodies in antibacterial serum is, as a rule, comparatively low. Ordinarily subcutaneous doses would hardly cause the circulating blood to act decisively on the invading germs. In fact, it would seem likely that the attempt to increase the antibodies in the blood-stream is not a good imitation of the curative processes of Nature in these cases, for in these, probably, much depends on the immunizing action of the body cells. In other cases a disturbing factor arises by reason of the extremely high specificity of the antibodies, so that not only must the latter arise from the same bacterial species as that against which they are used, but even the strains must be of the same class.

An attempt to correct this defect is made in the so-called "polyvalent" serums, in which several strains are used in immunizing the horse or other animal from which the serum is drawn. It must not be forgotten that there is no way in which the effectiveness of most of these serums can be accurately measured; and since the products of different establishments and of different horses in the same establishment vary widely in the content of antibodies which we know

and can measure, the lack of a potency standard here makes most uncertain the expectation of beneficial results from a given serum.

**ANTI-ANTHRAX SERUM.**—A serum prepared by immunizing horses against virulent anthrax bacilli.

*Actions and Uses.*—Good results have generally been reported from the use of the specific serum in human anthrax. Bactericidal and bacteriotropic properties are practically absent and the virtue of the serum may possibly be ascribed to an inhibition of capsule formation.

*Dosage.*—From 30 to 100 Cc. subcutaneously or intravenously. The serum should be used as early as possible and used freely, the dose being repeated several times a day in severe cases.

H. K. Mulford Co., Philadelphia.

*Anti-Anthrax Serum, Mulford.*—At least 80 to 100 Cc. should be injected intravenously as the initial dose. Marketed in packages containing two Mulford aseptic glass serum syringes of 10 Cc. each.

**ANTIDYSENTERIC SERUM.**—The blood serum of horses immunized against the Shiga bacillus and other forms of the dysentery bacillus.

*Actions and Uses.*—A reduction in the mortality rate of bacillary dysentery from 30 to 50 per cent. through the use of some serums has been reported by some observers but not confirmed by all. It would seem that the best results may be ascribed to an antitoxic action in infections with the Shiga-Kruse type of bacillus. Infections with the Flexner, Harris or Hiss-Y strains, which are relatively poor in toxin production, have not been so favorably affected, though some bactericidal action is claimed. The most favorable results are observed in the early stage of the disease.

The serum is required to show a high agglutinin titer for the various types of dysentery bacilli.

*Dosage.*—From 20 to 100 Cc. subcutaneously.

H. K. Mulford Co., Philadelphia.

*Antidysenteric Serum.*—From horses immunized against the Shiga, Flexner, and Y strains of the dysentery bacillus. Marketed in syringes containing 10 Cc. each; also in vials containing 50 Cc. each with sterile needle and sterile rubber tubing for intravenous injection.

*Dosage.*—Fifty to 100 Cc. to be followed at 8-hour intervals by doses of 50 Cc. until 400 Cc. are given. Prominent authorities recommend intravenous injection.

**ANTIGONOCOCCUS SERUM.**—A serum prepared by immunizing animals against the gonococcus.

*Actions and Uses.*—Serum therapy in gonorrheal arthritis has been reported by some as successful and by others as unsuccessful. The most favorable results have been reported in the joint complications of gonorrhea.

Little success has been achieved by the serum treatment of mucous membranes.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Antigonococcic Serum.*—Marketed in special syringes containing 10 Cc. each, with sterile needle.

Parke, Davis & Co., Detroit.

*Antigonococcic Serum.*—Prepared from the blood of rams immunized against both dead and living cultures of virulent gonococci according to the method of Rogers and Torrey (J. A. M. A., Sept. 14, 1907, p. 918). Marketed in bulbs containing 2 Cc. each.

E. R. Squibb & Sons, New York.

*Antigonococcic Serum.*—A highly immune polyvalent serum, prepared by immunizing horses against many strains of gonococci. Marketed in packages containing two 10 Cc. syringes.

**ANTIMENINGOCOCCUS SERUM.**—A serum prepared by the immunization of horses with virulent cultures of the meningococcus of Weichselbaum (*Diplococcus intracellularis*).

*Actions and Uses.*—Greater success has attended the use of serum directed against the meningococcus than has been the case with any other antibacterial serum. There is no question as to the marked reduction in mortality. The serum must be introduced into the subdural space and its action is due probably in part to bacteriotropins, possibly to anti-endotoxins and other antibodies as well. Each lot of the serum is required to be tested for potency by means of agglutination or complement fixation methods and none is allowed to be sold which does not reach a reasonable titer by at least one of the tests.

Each lot is tested at the Hygienic Laboratory prior to sale.

*Dosage.*—Average dose, 30 Cc. intraspinally as early as possible in the disease and repeated as indicated. The serum should be introduced slowly by gravity after the removal of a corresponding amount of cerebrospinal fluid. The administration of the serum should be controlled by blood pressure readings, a drop of 10 mm. mercury during administration being the signal for withdrawal of the needle.

Flexner's method of preparation consists in the inoculation of autolyzed cultures followed by living organisms.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)



*Antimeningococcus Serum (Antimeningitis Serum).*—Marketed in aseptic glass cylinders, of two sizes, containing respectively 15 and 30 Cc., each with special sterile needle and stylet; also in 20 Cc. vials.

Dosage: Usually from 5 to 15 Cc. for infants and children and 30 Cc. or more for adults are given at each dose, which should be repeated at twenty-four-hour intervals. The treatment of one case usually requires 120 Cc. or more.

H. K. Mulford Co., Philadelphia.

*Antimeningitis Serum.*—Marketed in aseptic ampules, each containing 15 Cc. with sterilized rubber tubing and sterilized intraspinal needle and stylet for injections by the gravity method.

Dosage: 15 to 30 Cc. at intervals of twenty-four hours.

E. R. Squibb & Sons, New York.

*Antimeningitic Serum.*—A polyvalent serum put up, two 15 Cc. in each package, in a special form of gravity container with needle and trocar.

**ANTIPNEUMOCOCCUS SERUM.**—A serum obtained from horses immunized by injection of virulent pneumococci. Each lot of antipneumococcic serum is submitted by the manufacturer to the U. S. Hygienic Laboratory for potency test before it is issued. It is required that 0.2 Cc. of the serum shall protect mice against 0.1 Cc. of a Type I culture that kills control mice in doses of 0.000001 Cc.

*Actions and Uses.*—Investigations indicate that the pneumococcus in lobar pneumonia may be referred to one of four types in respect to its response to serum treatment (Dochez and Gillespie: J. A. M. A., Sept. 6, 1913, p. 727). The serum used should be obtained from an animal immunized with pneumococci of the type corresponding to that present in the special case under treatment. Thus far Type I serum alone seems to be on reasonably secure clinical ground. Early massive (from 50 to 100 Cc.) intravenous doses of a highly potent serum, prepared from the type of pneumococcus present in the case to be treated are necessary.

Cutter Laboratory, Berkeley, Calif.

*Anti-Pneumococcic Serum, Type I.*—Marketed in vials containing 50 Cc.

The Gilliland Laboratories, Ambler, Pa.

*Antipneumococcic Serum, Type I.*—Marketed in vials containing 50 Cc.

Lederle Antitoxin Laboratories, New York (Schieffelin and Co., New York).

*Antipneumococcus Serum, Type I.*—Marketed in a pressure syringe containing 50 Cc.

H. K. Mulford Co., Philadelphia.

*Antipneumococcic Serum, Type I.*—Marketed in double ended vials containing 50 Cc.

*Antipneumococcic Serum, Polyvalent.*—Prepared by immunizing horses with dead and living pneumococci of the three fixed types (Types I, II, III) and standardized against Type I culture. It is of the same strength with regard to Type I as the Type I serum and in addition contains antibodies against Types II and III.

Marketed in double ended vials containing 50 Cc. each, with sterile needle and tubing for intravenous injection.

Parke, Davis and Co., Detroit.

*Antipneumococcic Serum, Type I.*—Marketed in a piston syringe containing 50 Cc.

E. R. Squibb and Sons, New York.

*Anti-Pneumococcic Serum, Type I.*—Marketed in vials containing 50 Cc.

**ANTISTREPTOCOCCUS SERUM.**—A serum obtained from horses immunized by the injection of killed or living cultures of streptococci.

*Actions and Uses.*—There is perhaps justification for the use of the serum in streptococcus infections; even then the result is doubtful. Bacteriotropins seem to be the principal antibodies present.

Burroughs Wellcome & Co., London, England, and New York.

*Polyvalent Antistreptococcus Serum.*—Obtained from horses injected with killed cultures of a number of strains from cases of erysipelas, scarlet fever, puerperal fever, rheumatism, septicemia, angina, pneumonia and ulcerative endocarditis.

*Antistreptococcus Serum (Erysipelas).*—Obtained from horses injected with killed cultures of a number of strains of streptococci obtained from cases of erysipelas.

*Antistreptococcus Serum (Rheumatism).*—Obtained from horses injected with killed cultures of a number of strains of streptococci obtained from cases of rheumatism.

*Antistreptococcus Serum (Scarlatina).*—Obtained from horses injected with killed cultures of a number of strains of streptococci obtained from cases of scarlet fever.

*Antistreptococcus Serum (Puerperal Fever).*—Obtained from horses injected with killed cultures of a number of strains of streptococci obtained from cases of puerperal fever.

All the foregoing are preserved with trikresol and are marketed in hermetically sealed vials containing in most cases from 25 to 50 Cc.

Cutter Laboratory, Berkeley, Calif.

*Antistreptococcic Serum.*—Marketed in piston syringe containers, each containing 10 Cc. of serum, and also in bottles containing 50 Cc.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Antistreptococcic Serum, Polyvalent.*—Marketed in aseptic glass cylinder containing 50 Cc. each, with sterile needle and rubber bulb connection, and in syringes containing 10 Cc. each.

Dosage: Prophylactic, 10 Cc.; curative, 20 to 100 Cc.

H. K. Mulford Co., Philadelphia.

*Antistreptococcic Serum, Polyvalent.*—The serum of horses which have been treated with streptococci of various strains. Marketed for immunizing purposes in syringes containing 10 Cc. and for therapeutic purposes in syringes containing 20 Cc.; also in ampules containing 50 Cc., with sterile needle and tubing for intravenous injection.

Dosage: 50 to 100 Cc. repeated at intervals of 4 to 6 hours. Prominent authorities recommend intravenous injection in malignant cases.

*Antistreptococcic Serum Scarlatinal, Polyvalent.*—The serum of horses which have been treated with streptococci taken from scarlet fever cases. Marketed in syringes containing 10 Cc. Also marketed in ampules containing 50 Cc., with sterile needle and tubing for intravenous injection.

Dosage: Prophylactic, 10 Cc.; curative, 50 to 100 Cc., repeated at intervals of 4 to 6 hours. Prominent authorities recommend intravenous injections in malignant cases.

Parke, Davis & Co., Detroit.

*Antistreptococcic Serum.*—A polyvalent serum prepared by immunizing horses with killed cultures of streptococci; the latter are obtained from various human streptococcus infections and certain pathologic conditions common to animals. Preserved with trikresol. Marketed in 10 Cc. piston syringe containers, also in bulbs containing 10 Cc. each.

E. R. Squibb & Sons, New York.

*Antistreptococcic Serum.*—A polyvalent serum obtained by immunizing horses with increasing doses of autolyzed cultures of streptococci and subsequently with live cultures. Marketed in packages of two syringes, each containing 10 Cc.; also in 20 Cc. vials, without a syringe.

*Antistreptococcus Serum Rheumaticus.*—Produced from strains of streptococcus from the joints and blood of cases of rheumatism. Intended for use in acute articular rheumatism.

Dosage: from 20 to 50 Cc., repeated in twenty-four hours, and again if necessary; administered intravenously, or subcutaneously if intravenous administration is impracticable.

## II.—Antigens Used for Prophylactic or Therapeutic Purposes

The use of substances for the production of active immunity has at least two advantages over the use of serums: The antibodies formed in the patient's own serum are not lost so rapidly as antibodies from the serum of another species, and, in the second place, not only are the immunity reactions of the blood serum made use of, but the fixed cells of the body may also take part in the immunizing process. Thus, protection from smallpox conferred by vaccination lasts for years, while the prophylactic action of diphtheria antitoxin is of avail only for days.

These advantages are frequently offset, however, by the tardiness and uncertainty with which active immunity appears and by the fact that the body may already be overloaded with antigen in the disease or that sufficient antigen to produce an effect would be in itself harmful to the patient.

Antigens may be of various sorts. Thus vaccine virus and antirabic virus, the two most notably successful, are conceded to be the living micro-organisms attenuated by passage through the bovine species in one instance and through the rabbit in the other. Other antigens, such as tuberculins and bacterial vaccines, consist of killed whole bacteria or of products formed by them or extracted from them.

#### A.—ATTENUATED LIVING VIRUSES

**VACCINE VIRUS.**—For description see the U. S. Pharmacopeia under *Virus Vaccinicum*.

Cutter Laboratory, Berkeley, Calif.

*Glycerinated Vaccine Virus.*—Marketed in packages containing respectively three and ten capillary tubes.

The Gilliland Laboratories, Ambler, Pa.

*Small-Pox Vaccine.*—Marketed in sealed capillary tubes, in packages containing one, five and ten tubes each.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Glycerinated Vaccine Virus.*—Protected from bacterial contamination by phenol and marketed in glass capillary tubes and in bulk (for 10, 20 or 50 vaccinations); also in wax capillary tubes.

H. K. Mulford Co., Philadelphia.

*Glycerinized Vaccine Lymph.*—Marketed in sealed capillary tubes with improved scarifying point; also on sterile glass points.

National Vaccine and Antitoxin Institute, Washington, D. C.

*Glycerinated Vaccine Virus.*—Marketed in capillary tubes; also on ivory points in special capsule.

Parke, Davis & Co., Detroit.

*Glycerinated Vaccine.*—Marketed in capillary tubes and on ivory points contained in sealed glass tubes provided with Lee's breakable ring so that they may be opened without difficulty.

E. R. Squibb and Sons, New York.

*Small-Pox (Variola) Vaccine (Glycerinated).*—Each dose in separate aseptic sealed glass tube, with bulb and needles. Boxes of 5 and boxes of 10 tubes.



**ANTIRABIC VACCINE.**—Antirabic vaccine or antirabic virus is the virus of rabies rendered practically nonvirulent for man by passage through a long series of rabbits and treated in various ways to decrease the infectivity still further. The method commonly in use in the United States is that of Pasteur as modified by the Hygienic Laboratory, Public Health Service: The spinal cords of the infected rabbits are dried over caustic potash at constant temperature for one to eight days, then cut into 0.5 cm. pieces and preserved in glycerine. For use, one of these pieces is emulsified in physiologic sodium chloride solution and injected into the subcutaneous tissue of the anterior abdominal wall. Injections are continued daily for twenty-one days. Other methods of treating the virus before inoculation are dilution (Högyes), emulsifying with 1 per cent. phenol (Fermi), drying at very low temperature (Harris), and dialyzing (Cummings).

*Actions and Uses.*—By treatment with antirabic vaccine after the bite of a rabid animal, immunity is usually established before the incubation period of the disease is concluded and rabies is thus prevented.

Dr. D. L. Harris' Laboratory, St. Louis (National Pathological Laboratories, Chicago).

*Rabies Vaccine (Harris).*—Brains and spinal cords of rabbits, dead of fixed virus rabies infection, are ground to a paste which is frozen in a container surrounded with carbon dioxide snow. The mass is pulverized and rapidly dried *in vacuo*. The resulting dry powder is standardized by the method devised by Dr. Harris, and stored *in vacuo* in the cold. One dose is given daily over a period of ten days or more, the early doses increasing in unitage up to a maximum. Each package contains vaccine and apparatus for the administration of one complete treatment, consisting of 10 tubes of rabies vaccine (Harris), sealed in a vacuum, and numbered consecutively; 10 vials containing sodium chloride solution for preparing the vaccine solution; and a Luer syringe with needle.

Laboratory of W. T. McDougall, Kansas City, Kan.

*Pasteur Antirabic Vaccine.*—The virus is prepared according to the method of the Hygienic Laboratory, Washington, D. C. An amount of the dried cord, sufficient for one dose, is emulsified in 50 per cent. glycerin accompanied by a syringe containing sterile physiologic salt solution for further dilution at the time of administration. A dose is sent daily by mail in a vacuum container. The treatment consists of twenty-one or twenty-five doses, according to the severity of the wound.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Rabies Vaccine.*—The vaccine is prepared according to the method of Pasteur. A complete treatment, consisting of twenty-five doses, is furnished. Each day an injection is shipped in a vacuum bottle. Complete description and directions accompany each outfit.

Eli Lilly and Company, Indianapolis, Ind.

*Pasteur Antirabic Preventive Treatment (Harris Modification).—*Brains and spinal cords of rabbits, dead of fixed virus rabies infection, are ground to a paste which is frozen by the addition of carbon dioxide snow. The mass is pulverized and rapidly dried in vacuo. The resulting dry powder is standardized by the method devised by Dr. Harris, and stored in vacuo in the cold. One dose is given daily over a period of 14 days, the early doses increasing in unitage up to a maximum. Supplied in emulsion in syringe ready for use. The first three doses are sent out from distributing stations, the remaining ones from the home office.

H. K. Mulford Co., Philadelphia.

*Rabies Vaccine.*—The vaccine is prepared according to the method of Pasteur. A complete treatment, consisting of twenty-five doses, is furnished. Each day an injection is shipped in a Caloris vacuum bottle. Complete description and directions accompany each outfit.

E. R. Squibb & Sons, New York.

*Pasteur Antirabic Vaccine.*—The virus is prepared according to the method of the Hygienic Laboratory, Washington, D. C. An amount of the dried cord sufficient for one dose is suspended in a mixture of 66 $\frac{2}{3}$  per cent. glycerin and 33 $\frac{1}{3}$  per cent. physiologic sodium chloride solution. The treatment consists of twenty-one daily treatments, each in an aseptic, sealed ampule, with syringe, packed in a Caloris container, which are sent daily by special delivery mail.

Pasteur Institute of St. Louis, St. Louis.

*Antirabic Vaccine.*—The virus is obtained from glycerinated brain substance. Marketed in 5 Cc. ampules. The treatment consists of eighteen doses which are sent by mail daily by special delivery, each dose being slightly larger than the preceding.

#### B.—TUBERCULINS

Many different methods have been used to prepare from the tubercle bacillus substances which might be used in the diagnosis, treatment or prophylaxis of tuberculosis. These have been, in general, called tuberculins and a few of the more prominent are enumerated here. For diagnosis Koch's Old Tuberculin is almost exclusively employed. For treatment, each tuberculin has its advocates, but it is doubtful if there is any essential difference in the immunizing action of the various forms. The strength varies, however, not only in tuberculins prepared by different methods, but also in different batches prepared in exactly the same manner. When a correct dosage for an individual has been found, therefore, a change to a different laboratory number of the same preparation should be accompanied by a reduction in the dose to one half in order to avoid a severe reaction. The plan of treatment provides usually for a gradual increase in dose, keeping the doses low enough to prevent any marked constitutional disturbance. For this reason the active cooperation of the patient is necessary and an accurate record must be kept of the temperature and pulse at frequent intervals during

the day and of the slightest change in subjective or objective symptoms. The immunity to tuberculin acquired by this increasing dosage is not an immunity to tuberculosis, but the advocates of this tuberculin treatment claim that it frequently is accompanied by clinical improvement. The usual hygienic-dietetic measures should be carried out as well.

*Danger from Tuberculins.*—The early history of the use of tuberculin is full of instances showing that it is a dangerous substance. The great risk lies in the chance of a severe reaction, and every precaution should be taken, both in diagnosis and in treatment, not to underestimate the patient's susceptibility to the tuberculin. This susceptibility varies enormously in different individuals and at different stages of the treatment, entirely out of relation to the progress of the disease. The use of tuberculin, therefore, requires special knowledge and experience.

**OLD TUBERCULIN.**—Tuberculin alt Koch.—Concentrated Tuberculin.—Crude Tuberculin.—Koch's original tuberculin is prepared from glycerin bouillon cultures of the tubercle bacillus by evaporating to one-tenth the original volume, sterilizing at 100 C. for one hour, and filtering through a Berkefeld filter. It is a clear brown syrupy liquid, with a high content of glycerin and a characteristic odor.

*Actions and Uses.*—For diagnosis, old tuberculin may be used by hypodermic injection to show a reaction at the site of application (local), at site of suspected disease (focal), or generally (constitutional). If positive, the tuberculin reaction merely indicates that the patient has at some time been infected with tuberculosis and not necessarily that he has clinical tuberculosis. Careful series of necropsies confirm the results of the use of tuberculin showing that perhaps 80 per cent. of adults have been infected with the tubercle bacillus, whether or not they have clinical tuberculosis requiring treatment. Moreover, in many advanced or acute cases of tuberculosis the patients do not react, so that the result of a tuberculin test is never absolute but always must be judged in the light of other findings. The occurrence of a focal reaction is good presumptive evidence of an active lesion.

For children, the cutaneous test has been chiefly used. This is performed by abrading the cleansed skin of the forearm in two places 2 inches apart through a drop of undiluted old tuberculin at each site; another similar abrasion is used as a control between the two; the two drops of tuberculin are carefully wiped off after ten minutes, allowing no tuberculin to touch the control site. The reaction consists in a zone of redness, usually with a papule, at the point of each tuberculin application, markedly larger than that at the control site. This reaction reaches its height in from twenty-four to forty-

eight hours. After infancy an increasing proportion of those who react are found to be free from clinical tuberculosis. The subcutaneous test is used more frequently on adults. A two-hour temperature chart should be kept for two days preceding and two days following each injection. To an adult in good condition 0.0002 Cc. may be given as the initial dose, and if there is no reaction 0.001 Cc. and then 0.005 Cc. may be tried. The doses should be at least three days apart and if there is the slightest suggestion of a reaction in temperature or symptoms the dose should be repeated, not increased. Children and weak patients should receive smaller doses, but no very weak patient and none with a fever should be subjected to the danger of a subcutaneous test. A rise of temperature of 1 degree Fahrenheit may be taken as a reaction, especially if accompanied by changes at the site of the disease. This reaction means, just as with the cutaneous test, only infection and not necessarily clinical tuberculosis; and owing to the danger of large doses, patients may fail to react because, though sensitive to tuberculin, they are not sensitive to doses small enough to be used safely.

For treatment, from 0.00000001 to 0.000001 Cc. may be used as the initial dose, and not more than two doses a week should be given.

Cutter Laboratory, Berkeley, Calif.

*Tuberculin for the Cutaneous Reaction (von Pirquet's Reaction).*—Marketed in packages containing three capillary tubes and in packages containing ten capillary tubes.

*Tuberculin Old (Tuberculin O. T.).*—In 1 Cc. vials, for use in solutions only. Also in serial dilutions; the latter packages containing 5 bottles each holding about 8 Cc., ranging from 0.01 to 100 mg. per Cc.

*Tuberculin O. T. Bovine.*—Made by the same process as the foregoing except that the organism used is of the bovine type.

*Tuberculin, Koch (concentrated).*—For the cutaneous reaction; in capillary pipettes.

*Tuberculin, Purified.*—1 per cent. solution, for the ophthalmic reaction.

*Tuberculin Ointment (Moro Ointment).*—A mixture of 50 per cent. each anhydrous wool fat and Tuberculin O. T., human strain.

Dosage: Varying amounts, usually about 0.2 Gm.

The Gilliland Laboratories, Ambler, Pa.

*Original Tuberculin, "O. T."*—Marketed in 1 Cc. vials.

*Tuberculin Ointment in Capsules (For the Moro Percutaneous Diagnostic Test).*—An ointment consisting of tuberculin "Old" and anhydrous wool fat equal parts. Marketed in capsules sufficient for one test.

H. K. Mulford Co., Philadelphia.

*Tuberculin "Old" (O. T.).*—Marketed in 1 Cc. vials; also in serial dilutions in 5 vials of 8 Cc. each, the first containing 0.001 mg. in each 2 minims, and each succeeding dilution being ten times stronger than the preceding.

Dosage: 2 minims.



*Von Pirquet Test for Tuberculosis.*—Old tuberculin marketed in capillary tubes, put up in packages of, respectively, one, three and ten tubes, each tube containing old tuberculin sufficient for one test, together with packages containing an equal number of tubes of concentrated glycerin bouillon for use as a control.

*Tuberculin Ointment (Moro Ointment).*—An ointment consisting of 50 per cent. of tuberculin "Old" with an equal part of adeps lanae hydrosus.

Parke, Davis & Co., Detroit.

*Tuberculin "Old" (Koch).*—Marketed in 0.5 Cc. bulbs.

*Tuberculin Discs for the Ophthalmic Reaction.*—Prepared by precipitating concentrated tuberculin with alcohol. Each disc contains 3.3 mg. tuberculin, which when dissolved in 0.3 Cc. (5 minims) of water makes a 1 per cent. solution.

**NEW TUBERCULIN, T. R.**—Tuberkelbacillin Rest, Koch.—Tuberculin Residue.—Tuberculin Rückstand.—This is made from living dried tubercle bacilli by thorough grinding, suspension in water and centrifuging. The supernatant fluid, containing extractives, is discarded and the sediment reground, suspended in a little water and recentrifuged. The fluid is kept this time, while the sediment is reground, suspended and centrifuged as before. This is repeated until practically no sediment remains, when all the fluid portions which have been laid aside are combined and diluted with 20 per cent. glycerin solution to make the final (standard) product contain the residue of 10 mg. of dried tubercle bacilli in each cubic centimeter of fluid.

T. R. in an uncolored slightly opalescent liquid. It is used occasionally in the treatment of tuberculosis.

Cutter Laboratory, Berkeley, Calif.

*Tuberculin T. R.*—Tubercle Residue.—A suspension of 2 mg. of tubercle substance in each Cc. of the finished product.

Dosage: From 0.001 mg. to 100 mg. or more of the fluid T. R.

The Gilliland Laboratories, Ambler, Pa.

*Tuberculin Residue, "T. R."*—Marketed in 1 Cc. and 3 Cc. vials; preserved with 0.4 per cent. trikresol.

H. K. Mulford Co., Philadelphia.

*Tuberculin "R."*—Marketed in 1-Gm. vials and in serial dilutions of graduated strengths.

Parke, Davis & Co., Detroit.

*Tuberculin T. R.*—Marketed in 1 Cc. bulbs in 2 strengths; one contains 0.001 mg. of tubercle solids per Cc., the other 1 mg. per Cc.

**NEW TUBERCULIN, B. E.**—Bazillenemulsion, Koch.—Bacilli Emulsion.—Bacilli emulsion is practically a bacterial vaccine. It is made by suspending one part pulverized tubercle bacilli in 100 parts distilled water and 100 parts glycerin. This mixture stands one day and is then decanted from the grosser particles which have settled. One cubic centimeter thus corresponds to 5 mg. of tubercle bacilli.

It is a white, fairly permanent emulsion, but should be shaken thoroughly before making dilutions. B. E. is used in the therapeutics of tuberculosis probably more frequently than any other tubercle preparation.

Cutter Laboratory, Berkeley, Calif.

*Tuberculin Bacillen Emulsion.*—Tuberculin B. E.—A suspension of ground tubercle bacilli containing 5 mg. of the solid tubercle substance to each Cc.

Dosage: From 0.001 mg. to 100 mg. or more of the fluid B. E. Tuberculin.

*Tuberculin B. E. Bovine.*—A suspension similar to the foregoing, except that the tubercle bacillus used is of the bovine type.

The Gilliland Laboratories, Ambler, Pa.

*Bacillen Emulsion Tuberculin, "B. E."*—Marketed in 1 Cc. and 3 Cc. vials; preserved with 0.4 per cent. trikresol.

H. K. Mulford Co., Philadelphia.

*Bacillin Emulsion "B. E."*—Marketed in 1-Cc. vials; also in serial dilutions.

Parke, Davis & Co., Detroit.

*Tuberculin B. E. (concentrated).*—Bacillus Emulsion, marketed in bulbs containing 1 mg. of dry tubercle solids per Cc.

*Moist Dead Tubercle Germs.*—For use in making the bacillary emulsion for the tuberculo-opsonic test.

**TUBERCULIN DENYS, B. F.**—Bouillon Filtré.—Bouillon Filtrate.—This is prepared like old tuberculin without the prolonged heating and concentration; that is, it is simply a glycerin-broth culture of the tubercle bacillus, passed through a porcelain filter; it contains all the soluble products of the growth of the tubercle bacillus.

Cutter Laboratory, Berkeley, Calif.

*Tuberculin B. F. (Bouillon Filtrate).*—In 1-Cc. vials; preserved with trikresol; for use in dilutions only. Also in serial dilutions.

*Tuberculin B. F. Bovine.*—Made in the same manner except that the bovine type of tubercle bacillus is used.

The Gilliland Laboratories, Ambler, Pa.

*Bouillon Filtrate Tuberculin*, "B. F."—Marketed in 1 Cc. and 3 Cc. vials; preserved with 0.4 per cent trikresol.

H. K. Mulford Co., Philadelphia.

*Tuberculin, Bouillon Filtrate, Denys*.—Marketed in 1-Cc. vials; also in serial dilutions.

Parke, Davis & Co., Detroit.

*Tuberculin B. F.*—Marketed in 1-Cc. bulbs; contains 0.4 per cent. trikresol.

**DETRE DIFFERENTIAL TEST.**—By vaccinating by Pirquet's method at the same time with old tuberculin, human bacilli filtrate and bovine bacilli filtrate and measuring the size of the respective papules produced, Detre claims to be able to determine whether the patient is infected with human or bovine tubercle bacilli and whether the disease is active or latent. The theoretical basis of this test is not thoroughly established and many observers regard it as of little or no practical value.

Cutter Laboratory, Berkeley, Calif.

*Detre Differential Test*.—Made up of one tube each of Tuberculin O. T., Tuberculin B. F. human, Tuberculin B. F. bovine. Each tube contains about 0.1 Cc.

The Gilliland Laboratories, Ambler, Pa.

*Tuberculin for the Detre Differential Diagnostic Test*.—Consisting of one tube each of Original Tuberculin "O. T.", Bouillon Filtrate Tuberculin "B. F." human, and Bouillon Filtrate Tuberculin "B. F." bovine.

#### C.—BACTERIAL VACCINES

Bacterial vaccines, or bacterins, are suspensions of killed bacteria in physiologic saline solution, usually with the addition of some preservative such as 0.4 per cent. trikresol or 0.5 per cent. phenol.

The use of bacterial vaccines is associated with the development of the opsonic theory, but the value of the opsonic index as a measure of immunity is open to question and at present the determination of the index is rarely made. Bacterial vaccines probably are of value in localized staphylococcus infections. Good results have also been reported in localized chronic nonurethral gonococcic diseases, such as gonorrheal bacillus, are said to have been much improved. Irregular but somewhat encouraging reports are made of the use of the acne bacillus of Unna and Sabouraud. Koch's bacilli emulsion tuberculin is used as a bacterial vaccine in tuberculosis.

The therapeutic use of stock bacterial vaccines rests on uncertain clinical evidence—the favorable reports should be

viewed with recognition of the perhaps unconscious bias to which some users of new remedies are prone. No marked and uniform beneficent results have been authoritatively confirmed.

Any successful bacterial therapy depends, first of all, on an accurate bacteriologic diagnosis; next in importance is the use of an "autogenous" vaccine; that is, one made from the strain isolated from the patient. If this is not practicable, stock vaccine may be used; though in some cases, such as colon infections, the autogenous strain seems to be necessary. Few clinicians of standing use stock vaccines.

The dosage and intervals for bacterial vaccine treatment cannot be stated definitely. In general, the severer the disease, the smaller the dose should be, and the smaller the doses, the shorter the intervals. In mild affections no improvement may result until the vaccine is pushed to a systemic reaction. With the staphylococcus it is safe to begin with 50,000,000 killed bacteria and four-day intervals, increasing to a billion or more. With colon bacillus, pneumococcus, and acne bacillus, 5,000,000 is a low initial dose; gonococci and streptococci should be given in even less amounts. If a "negative phase" and reaction be produced with any vaccine, the interval should be lengthened to seven or ten days.

Prophylactically, the typhoid vaccine has proved of great value. Plague and cholera vaccines are also used in prophylaxis; but, except for travelers, general sanitary measures should be used instead of individual immunization.

**ACNE BACILLUS VACCINE.**—Prepared from the acne bacillus of Unna and Sabouraud.

*Actions and Uses.*—The acne bacillus is not found in all cases of acne, but in those cases in which the bacillus is found it seems to be the active pathogenic agent and the use of acne vaccine may give good results. In other cases the staphylococcus is responsible for the inflammation and the corresponding staphylococcus vaccine may be tried. If both organisms are present a mixture of the two vaccines may be indicated, but the use of a ready prepared mixed vaccine is not rational as a routine treatment.

The Abbott Laboratories, Chicago.

*Acne Bacteria, Polyvalent.*—Marketed in syringes containing respectively 25, 50, 100 and 200 million killed acne bacilli; also in packages of six ampules each containing 50 million killed acne bacilli.

Cutter Laboratory, Berkeley, Calif.

*Acne Bacillus Vaccine.*—Acne Bacillus Bacteria.—Each cubic centimeter contains 50 million killed acne bacilli suspended in physiologic salt solution with 0.4 per cent. trikresol.

Dosage: From 5 to 50 million killed bacteria.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)



*Acne Vaccine*.—Marketed in syringes containing respectively 5, 10, 20, 40 and 100 million killed acne bacteria; also in packages of four syringes, containing respectively 5, 10, 20 and 40 million killed bacteria; also in sets of four packages of two vials each, containing respectively 5, 10, 20 and 40 million killed bacteria; also in 20-Cc. vials in four strengths, 1 Cc. containing respectively 5, 10, 20 and 40 million acne bacilli.

H. K. Mulford Co., Philadelphia.

*Acne Bacterin*.—Marketed in syringes containing respectively 25, 50, 100 and 200 million killed acne bacilli, sold in a package of four syringes or as separate syringes; in packages of two 1-Cc. ampules, each containing 25 million killed bacteria; in packages of two 1-Cc. ampules each containing 200 million killed bacteria; in 5-Cc. vials containing 25 million killed bacteria per Cc.; in 5-Cc. vials containing 200 million killed bacteria per Cc., and in 20-Cc. vials containing 50 million killed bacteria per cubic centimeter.

Dosage: Initially 5 to 25 million.

Parke, Davis & Co., Detroit.

*Acne Vaccine*.—Marketed in packages of four bulbs, each bulb containing 100 million bacteria sterilized with heat and ready for use.

E. R. Squibb & Sons, New York.

*Acne Vaccine*.—Marketed in boxes of 4 syringes containing 25, 50, 100 and 200 million killed bacilli. Also in boxes of 2 syringes containing 50 and 200 million killed bacilli; boxes of 6 ampules containing 10, 25, 50, 100, 200 and 500 million killed bacilli, with a syringe; and boxes of 2 ampules containing 50 and 200 million killed bacilli, with a syringe.

**CHOLERA VACCINE**.—Prepared from killed cholera vibrios.

*Actions and Uses*.—Cholera vaccine has been used as a prophylactic with generally favorable results.

H. K. Mulford Co., Philadelphia.

*Cholera Bacterin (Cholera Vaccine)*.—Marketed in packages of three syringes each, the first containing 500 million killed cholera vibrios, while the second and third each contain 1,000 million killed vibrios.

**COLON BACILLUS VACCINE**.—Made from *Bacillus coli communis*.

*Actions and Uses*.—The colon bacillus in a special strain is the cause of many cases of cystitis and pyelonephritis. The use of an autogenous vaccine is often highly successful in the treatment of these affections. Stock vaccines have not pro-

duced good results. If a stock vaccine must be used, it should be polyvalent so that the special strain needed may be included if possible.

The Abbott Laboratories, Chicago.

*Coli Bacterin, Polyvalent*.—Marketed in syringes containing respectively 50, 100, 200 and 400 million killed colon bacilli; also in packages of six ampules, each containing 100 million killed colon bacilli.

Cutter Laboratory, Berkeley, Calif.

*Colon Bacillus Vaccine*.—A suspension of *B. coli communis* in physiologic salt solution with 0.4 per cent. trikresol, containing 50 million killed bacilli per cubic centimeter.

Dosage: From 10 to 100 million.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Colon Vaccine*.—Marketed in four packages of two vials each containing respectively 50, 100, 200 and 400 million killed bacilli.

*Colon Vaccine, Polyvalent*.—Marketed in 1-Cc. vials and in syringes containing respectively 50, 100, 200 and 400 million killed bacilli, also in 20-Cc. vials in four strengths, 1 Cc. containing respectively 50, 100, 200 and 400 million killed bacilli.

H. K. Mulford Co., Philadelphia.

*Coli Bacterin*.—Marketed in packages of four graduated syringes, containing respectively 50, 100, 200 and 400 million killed colon bacilli (sold also in single syringes); in packages of two 1-Cc. ampules, each containing 50 million killed colon bacilli; in packages of two 1-Cc. ampules, each containing 400 million killed colon bacilli; in 5 Cc. ampules, each containing 50 million killed colon bacilli per cubic centimeter; in 5-Cc. ampules, each containing 400 million killed colon bacilli per cubic centimeter; in 20-Cc. vials containing 50 million killed colon bacilli per cubic centimeter.

Parke, Davis & Co., Detroit.

*Colon Vaccine*.—Marketed in packages of four bulbs, each bulb containing 200 million bacteria sterilized with heat and ready for use.

E. R. Squibb & Sons, New York.

*Bacillus Coli Communis Vaccine*.—Marketed in boxes of 4 syringes containing 100, 200, 500 and 1,000 million killed bacilli. Also boxes of 2 syringes containing 100 and 500 million killed bacilli and boxes of 2 ampules containing 100 and 500 million killed bacilli, with a syringe; also in boxes of 6 ampules of which 2 contain each 100 million, 2 each 500 million and 2 each 1,000 million killed bacilli, with a syringe.

**FRIEDLAENDER BACILLUS VACCINE**.—Made from *Bacillus pneumoniae*, which is found in the nasal secretion or sputum in some nasal or respiratory disorders.

The Abbott Laboratories, Chicago.

*Friedländer Bacterin, Polyvalent.*—Marketed in syringes, containing respectively 50, 100, 200 and 400 million killed Friedländer bacilli; also in packages of six ampules each containing 100 million killed Friedländer bacilli.

**GONOCOCCUS VACCINE.**—Made from *Micrococcus gonorrhoeae*.

*Actions and Uses.*—Clinical experience has presented no clear evidence of the value of gonococcal vaccine in affections of the mucous surfaces. As a prophylactic against metastatic complications it may have some value. Many observers believe that these vaccines are useful in arthritis. The value of vaccines in gonococcal pelvic lesions is not clearly determined. They are of little if any value in gonococcal sepsis or in gonococcemia.

The Abbott Laboratories, Chicago.

*Gonococcus Bacterin, Polyvalent.*—Marketed in syringes, containing respectively 50, 100, 200 and 400 million killed gonococci; also in packages of six ampules, each containing 100 million killed gonococci.

Cutter Laboratory, Berkeley, Calif.

*Gonococcic Vaccine.*—Marketed in 1-Cc. vials, each cubic centimeter containing about 500 million cocci suspended in physiologic sodium chloride solution with 0.4 per cent. trikresol.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Gonococcus Vaccine, Polyvalent.*—Marketed in 1-Cc. vials and in syringes, containing respectively 50, 100, 200 and 400 million killed gonococci; also in 20-Cc. vials in four strengths, 1 Cc. containing respectively 50, 100, 200 and 400 million killed gonococci; also in separate syringe packages containing respectively 50, 100, 200, 400 and 1,200 million killed gonococci.

H. K. Mulford Co., Philadelphia.

*Neisser Bacterin.*—Marketed in packages of four syringes (which are also sold singly), containing respectively 50, 100, 200 and 400 million killed gonococci; in packages of two 1-Cc. ampules, each containing 50 million killed gonococci; in packages of two 1-Cc. ampules, each containing 400 million killed gonococci; in 5-Cc. vials containing 50 million killed gonococci per cubic centimeter; in 5-Cc. vials containing 400 million killed gonococci per cubic centimeter, and in 20-Cc. vials, each cubic centimeter containing 500 million killed gonococci.

National Vaccine and Antitoxin Institute, Washington, D. C.

*Gonococcic Vaccine.*—Marketed in syringes, each said to contain 2 million to 50 million bacteria; sterilized by heat.

Parke, Davis & Co., Detroit.

*Gonococcus Vaccine*.—Marketed in bulbs, each said to contain 20 million bacteria; sterilized by heat.

G. H. Sherman, Detroit.

*Gonococcus Vaccine*.—Each cubic centimeter is said to contain one billion killed gonococci.

E. R. Squibb & Sons, New York.

*Gonococcus Vaccine*.—Marketed in boxes of 4 syringes containing 100, 200, 350 and 500 million killed gonococci. Also in boxes of 2 syringes containing 100 and 500 million killed gonococci; boxes of 6 ampules containing 50, 100, 150, 350, 500 and 1,000 million killed gonococci, with a syringe; and boxes of 2 ampules containing 100 and 500 million killed gonococci, with a syringe.

**MENINGOCOCCUS VACCINE**.—Made from *Diplococcus intracellularis meningitidis* of Weichselbaum.

*Actions and Uses*.—Meningococcus vaccine has been used on a limited scale with apparent success for the prevention of epidemic cerebrospinal meningitis.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Meningococcus Vaccine*.—Marketed in packages containing three syringes, the first containing 500 million killed meningococci, while the second and third contain each 1,000 million killed meningococci. The contents of these syringes should be injected subcutaneously at intervals of ten days. Also marketed in packages containing three vials each, the first containing 500 million and the second and third containing each 1,000 million killed meningococci.

H. K. Mulford Company, Philadelphia.

*Meningo-Bacterin*.—Marketed in packages of three syringes, one containing 500 million, and the second and third each 1,000 million killed meningococci. For the first injection 500 million killed meningococci are used and the second and third injections are made at ten-day intervals. Put up in two styles: (a) in packages containing each dose in a separate syringe intended for the immunization of one individual and (b) in packages containing thirty ampules of ten complete immunizing doses. The successive doses are distinguished by red, white and blue labels. No syringe is contained in this package.

G. H. Sherman, Detroit.

*Meningococcus Vaccine*.—Each cubic centimeter contains about 1,000 million killed meningococci.

E. R. Squibb & Sons, New York.

*Meningococcus Vaccine, Immunizing*.—Marketed in boxes of 3 syringes containing 100, 500 and 1,000 million killed meningococci, and in boxes of 3 ampules, containing respectively 100, 500 and 1,000 million killed meningococci with a syringe.



*Meningococcus Vaccine, Curative.*—Marketed in boxes of 4 syringes containing 100, 200, 400 and 500 million killed meningococci. Also in boxes of 2 syringes containing 100 and 500 million killed meningococci; boxes of 6 ampules, 2 containing each 100 million, 2 each 500 million, and 2 each 1,000 million killed meningococci, with a syringe, and boxes of 2 ampules containing 100 and 500 million killed meningococci, with a syringe.

**PERTUSSIS BACILLUS VACCINE.**—Made from the bacillus of whooping-cough, isolated first by Bordet and Gengou.

*Actions and Uses.*—The evidence indicates that it may be of value both for prevention and treatment, although the reports are conflicting.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Pertussis Vaccine.*—Marketed in syringes, containing respectively 25, 50, 100 and 200 million killed Bordet-Gengou bacilli; also in sets of four packages of two vials each, containing respectively 25, 50, 100 and 200 million killed bacteria; also in 20-Cc. vials in four strengths, 1-Cc. containing respectively 25, 50, 100 and 200 million pertussis bacilli.

H. K. Mulford Company, Philadelphia.

*Pertussis Bacterin-Mulford.*—Marketed in boxes of 4 syringes containing 50, 100, 200 and 400 million killed Bordet-Gengou bacilli.

E. R. Squibb & Sons, New York.

*Bacillus Pertussis Vaccine.*—Marketed in boxes of 4 syringes containing 25, 50, 100 and 200 million killed bacilli. Also boxes of 2 syringes containing 50 and 200 million killed bacilli; boxes of 6 ampules containing 25, 50, 100, 200, 300 and 500 million killed bacilli, with a syringe; and boxes of 2 ampules containing 50 and 200 million killed bacilli, with a syringe.

**PLAGUE BACILLUS VACCINE.**—Made from *Bacillus pestis*.

*Actions and Uses.*—Vaccine has been used for the prevention of plague with results justifying its use but owing to the acute nature of the disease time is not allowed for the development of active immunity after actual infection. No practical application therefore has been made of vaccine treatment in plague.

H. K. Mulford Co., Philadelphia.

*Plague Bacterin.*—Marketed as follows: I. Single-dose vaccination in 1-Cc. ampules. Standardized to contain 5,000 million killed plague bacilli in each cubic centimeter. II. Ten single-dose vaccinations in one 10-Cc. ampule. Standardized to contain 5,000 million killed plague bacilli in each cubic centimeter. III. Single two-dose vaccination in two 1-Cc. ampules. Two vaccinations are used for one immunization. The first

dose (red label) is standardized to contain 1,000 million and the second dose (white label) to be injected from seven to ten days later, or when the reaction to the first injection has subsided, is standardized to contain 2,000 million killed plague bacilli in each cubic centimeter. IV. Ten two-dose vaccinations in two 10-Cc. ampules. Each cubic centimeter of ampule with red label, marked "First vaccination," is standardized to contain 1,000 million killed plague bacilli. Each cubic centimeter of ampule with white label marked "Second vaccination," is standardized to contain 2,000 million killed organisms.

**PNEUMOCOCCUS VACCINE.**—Made from *Diplococcus pneumoniae*.

A vaccine or "antigen" is prepared by E. C. Rosenow (J. A. M. A., March 16, 1918, p. 759) by digesting a suspension of pneumococci at 37 C. until about 95 per cent. of the organisms have become gram-negative and the mixture is relatively nontoxic to guinea-pigs.

**Actions and Uses.**—The value of vaccination in the treatment of pneumonia is very doubtful. The results of the prophylactic use of the vaccine is more encouraging. There is evidence that the use of vaccine alone or in conjunction with antipneumococcus serum is of advantage in the treatment of ulcer corneae repens, an affection which is caused by pneumococcus.

E. C. Rosenow believes that the protective power against pneumococcus infection is greater with a vaccine prepared according to his method than that of a vaccine made according to the usual method.

The Abbott Laboratories, Chicago.

**Pneumo-Bacterin, Polyvalent.**—Marketed in syringes, containing respectively 50, 100, 200 and 400 million killed pneumococci; also in packages of six ampules, each containing 100 million killed pneumococci.

Cutter Laboratory, Berkeley, Calif.

**Pneumococcic Vaccine.**—**Pneumococcic Bacterin.**—A suspension of mixed strains of *Diplococcus pneumoniae* in physiologic salt solution with 0.4 per cent. trikresol, containing 50 million killed pneumococci in each cubic centimeter.

Dosage: From 10 to 100 million.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

**Pneumococcus Vaccine, Polyvalent.**—Marketed in vials and in syringes containing respectively 50, 100, 200 and 400 million killed pneumococci; also in 20-Cc. vials in four strengths, 1-Cc. containing respectively 50, 100, 200 and 400 million killed pneumococci.

Eli Lilly & Co., Indianapolis.

**Pneumococcus Antigen (Rosenow), Lilly.**—Marketed in 5 Cc. vials, each cubic centimeter containing 20 billion partially autolyzed pneumococci.

H. K. Mulford Co., Philadelphia.

*Pneumo-Bacterin*.—Each cubic centimeter is said to contain about 50 million killed pneumococci. Marketed in packages of four syringes (which may also be obtained separately) containing respectively 50, 100, 200 and 400 million killed pneumococci; also in packages of four 1-Cc. ampules, each containing 50 million killed pneumococci; also in 20-Cc. vials, each containing 50 million killed pneumococci.

E. R. Squibb & Sons, New York.

*Pneumococcus Vaccine*.—Marketed in boxes of 4 syringes containing respectively 100, 200, 400 and 500 million killed pneumococci; boxes of 2 syringes containing respectively 100 and 500 million killed pneumococci; boxes of six ampules, two containing each 100 million, two each 500 million and two each 1,000 million killed pneumococci, with a syringe, and boxes of two ampules containing 100 and 500 million killed pneumococci, with a syringe.

**STAPHYLOCOCCUS VACCINES.**—Made from *Staphylococcus pyogenes aureus*, from *Staphylococcus pyogenes albus*, or from *Staphylococcus pyogenes citreus*, or from all three.

*Actions and Uses*.—*Staphylococcus vaccine* is used in carbuncle, furunculosis, sycosis, and certain cases of acne. An autogenous vaccine is preferable, but if this cannot be made, a stock vaccine can be used with good prospect of success. The forms of acne most likely to respond are characterized by deep-seated pustules, with considerable induration, situated on the face, chest and back. When the lesions are superficial and indolent, the acne vaccine may give good results, and when there is a mixture of active and indolent lesions, a mixture of the two vaccines may be used.

The Abbott Laboratories, Chicago.

*Staphylo-Albus-Bacterin, Polyvalent*.—Marketed in syringes, containing respectively 200, 400, 800 and 1,000 million killed staphylococci; also in packages of six ampules, each containing 200 million killed staphylococci.

*Staphylo-Aureus-Bacterin, Polyvalent*.—Marketed in syringes containing respectively 200, 400, 800 and 1,000 million killed organisms of this type; also in packages of six ampules, each containing 200 million killed organisms.

*Staphylo-Bacterins (Human) Albus-Aureus-Citreus*.—Marketed in four syringes containing respectively 200, 400, 800 and 1,000 million killed bacteria; also in packages of six ampules, each containing 200 million killed bacteria.

Cutter Laboratory, Berkeley, Calif.

*Staphylococcic Vaccine*.—A suspension of various strains of *Staphylococcus aureus*, *albus* and *citreus* in physiologic sodium chloride solution with 0.4 per cent. trikresol, containing about 500 million to each cubic centimeter.

Dosage: From 100 million to 1,000 million killed bacteria.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Staphylococcus Vaccine, Polyvalent*.—Marketed in vials and in syringes containing respectively 250, 500, 1,000 and 2,000 million killed staphylococci; also in 20-Cc. vials in four strengths containing respectively 250, 500, 1,000 and 2,000 killed staphylococci per cubic centimeter.

*Staphylococcus Albus Vaccine, Polyvalent*.—Marketed in vials and in syringes containing respectively 250, 500, 1,000 and 2,000 million killed bacteria; also in 20-Cc. vials in four strengths, containing respectively 250, 500, 1,000 and 2,000 million killed staphylococci of the type named per cubic centimeter.

*Staphylococcus Aureus Vaccine, Polyvalent*.—Marketed in vials and in syringes containing respectively 250, 500, 1,000 and 2,000 million killed bacteria; also in 20-Cc. vials in four strengths, containing respectively 250, 500, 1,000 and 2,000 million killed organisms per cubic centimeter.

H. K. Mulford Co., Philadelphia.

*Staphylo-Albus Bacterin*.—Marketed in packages of four syringes (which may also be obtained singly), containing respectively 250, 500, 1,000 and 2,000 million killed staphylococci; also in packages of six 1-Cc. ampules, each containing 250 million killed cocci; and in 20-Cc. vials, containing 250 million killed cocci per cubic centimeter.

*Staphylo-Aureus Bacterin*.—Marketed in packages of four syringes (which may also be obtained singly), containing respectively 250, 500, 1,000 and 2,000 million staphylococci of the type named; also in packages of six 1-Cc. ampules, each containing 250 million killed organisms; and in 20-Cc. vials, containing 250 million killed organisms per cubic centimeter.

*Staphylo-Bacterin*.—Marketed in packages of four syringes (which may also be obtained singly), containing respectively 250, 500, 1,000 and 2,000 million killed bacteria (a mixed culture of *Staphylococcus albus* and *aureus*); in packages of two 1-Cc. ampules, each containing 250 million killed bacteria; in packages of two 1-Cc. ampules, each containing 2,000 million killed bacteria; in 5-Cc. vials containing 250 million killed bacteria per cubic centimeter; in 5-Cc. vials containing 2,000 million killed bacteria per cubic centimeter; and in 20-Cc. vials containing 250 million killed bacteria per cubic centimeter.

Parke, Davis & Co., Detroit.

*Staphylococcus Vaccine (Albus)*.—Supplied in dilutions of 400 and 1,000 million per Cc.; marketed in packages containing four bulbs each; also in packages containing respectively one and four containers.

*Staphylococcus Vaccine (Aureus)*.—Supplied in dilutions of 400 and 1,000 million per Cc.; marketed in packages containing four bulbs each; also in packages containing respectively one and four syringe containers.

*Staphylococcus Vaccine (Citreus)*.—Supplied in dilutions of 400 and 1,000 million per Cc.; marketed in packages containing four bulbs each; also in packages containing respectively one and four syringe containers.

*Staphylococcus Vaccine (Combined) Albus, Aureus and Citreus*.—Supplied in dilutions of 400 and 1,000 million per cubic centimeter; marketed in packages containing four bulbs each; also in packages containing respectively one and four syringe containers.



*Furunculosis Vaccine*.—Made from strains of staphylococci of the different varieties, obtained from furuncular lesions; supplied in dilutions of 400 million per cubic centimeter; marketed in packages containing four bulbs each; also in packages containing respectively one and four syringe containers.

G. H. Sherman, Detroit.

*Staphylococcus Pyogenes Albus and Aureus Vaccine*.—A mixed vaccine containing one billion killed organisms of the varieties named in each cubic centimeter.

E. R. Squibb & Sons, New York.

*Staphylococcus Vaccine*.—Marketed in boxes of 4 syringes containing 100, 200, 500 and 1,000 million killed staphylococci; also in boxes of 2 syringes containing 100 and 500 million killed staphylococci; boxes of 6 ampules containing 100, 250, 500, 500, 1,000 and 2,000 million killed staphylococci, with a syringe, and boxes of 2 ampules containing 100 and 500 million killed staphylococci, with a syringe.

Swan-Myers Company, Indianapolis.

*Swan's Staphylococcus Bacterin (No. 37)*.—Marketed in packages of six 1 Cc. vials, also in 20 Cc. vials, each containing 1,000 million killed organisms per cubic centimeter of the *Staphylococcus pyogenes albus* type.

**STREPTOCOCCUS VACCINE**.—Made from different strains of *Streptococcus pyogenes* isolated from phlegmon, from the throat, from scarlet fever, from erysipelas, etc.

*Actions and Uses*.—Streptococci are known to be the cause of various septic conditions and processes due to them may complicate scarlet fever and other contagious diseases. In cases of localized sepsis, a vaccine made from the organisms causing the septic condition in the particular case is frequently useful. For this purpose an autogenous streptococcus vaccine may be useful in abscess, the septic complications of scarlet fever, such as otitis, etc. The use of vaccines in cases of chronic deforming arthritis has met with some success, but it is a mistake to rely largely on them. Stock vaccines, being less directly related to the cause of disease, afford less prospect of success than autogenous.

Streptococcus vaccines have been suggested for the prevention of scarlet fever and for the treatment of scarlet fever, puerperal fever, acute rheumatism, ulcerative endocarditis, etc., but clinical experience affords no sufficient evidence of their value in these conditions. There is reason to believe that in conditions of general sepsis large doses of vaccines may be directly harmful.

The Abbott Laboratories, Chicago.

*Strepto-Bacterin (Human), Polyvalent*.—Marketed in syringes containing respectively 50, 100, 200 and 400 million killed streptococci; also in packages of six ampules, each containing 100 million killed bacteria.

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Cutter Laboratory, Berkeley, Calif.

*Streptococcic Vaccine*.—*Streptococcic Bacterin*.—A suspension containing in each cubic centimeter 50 million of killed streptococci in physiologic sodium chloride solution with 0.4 per cent. trikresol.

Dosage: From 5 to 50 million.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Streptococcus Vaccine, Polyvalent*.—Marketed in vials and in syringes containing respectively 50, 100, 200 and 400 million killed streptococci; also in 20-Cc. vials in four strengths, containing respectively 50, 100, 200 and 400 million killed streptococci.

H. K. Mulford Co., Philadelphia.

*Strepto-Bacterin*.—Marketed in packages of four syringes (which are also sold singly), containing respectively 50, 100, 200 and 400 million killed streptococci; also in packages of two 1-Cc. ampules, containing 250 million killed streptococci, and in packages of two 1-Cc. ampules, each containing 400 million killed streptococci; also in 20-Cc. vials, each cubic centimeter containing 50 million killed streptococci.

Parke, Davis & Co., Detroit.

*Streptococcus Vaccine*.—Each cubic centimeter contains about 40 million killed streptococci.

G. H. Sherman, Detroit.

*Streptococcus Pyogenes Vaccine*.—Each cubic centimeter is said to contain 400 million killed streptococci.

E. R. Squibb & Sons, New York.

*Streptococcus Vaccine*.—Marketed in boxes of 4 syringes containing 100, 200, 500 and 1,000 million killed streptococci; also in boxes of 2 syringes containing 100 and 500 million killed streptococci; boxes of 2 ampules containing 100 and 500 million killed streptococci, with a syringe; also in boxes of six ampules, two containing each 100 million, two each 500 million and two each 1,000 million killed streptococci, with a syringe.

Swan-Myers Company, Indianapolis.

*Swan's Streptococcus Bacterin (No. 43)*.—Marketed in packages of six 1-Cc. vials, also in 20-Cc. vials, each containing 200 million killed streptococci per cubic centimeter.

**TYPHOID VACCINE**.—Made from *Bacillus typhosus*. In some cases *Bacillus paratyphosus A* and *Bacillus paratyphosus B* are also used.

*Actions and Uses*.—Typhoid vaccine is of recognized utility in the prevention of typhoid fever. The immunity produced persists in the majority of cases from two to four years or longer. The vaccine may be used in treatment of typhoid

carriers. In such cases an autogenous vaccine is to be preferred. The same is true in the bacterial complications and sequelæ of typhoid fever, especially those that appear during convalescence or are prolonged into that stage.

The use of vaccine in the treatment of typhoid fever has given very inconclusive results.

*Dosage.*—As a preventive typhoid vaccine should be administered only to healthy persons. The skin should be sterilized with iodine and an initial dose of 500,000,000 bacteria injected with aseptic precautions. This injection should be followed in from seven to ten days by a second dose of 1,000,000,000 bacteria and a third injection of the same size is given seven to ten days after the second.

The Abbott Laboratories, Chicago.

*Typho-Bacterin, Polyvalent.*—Marketed in syringes containing, respectively, 100, 200, 400 and 800 million killed typhoid bacilli; also in packages of six ampules, each containing 200 million killed typhoid bacilli.

*Typhoid Prophylactic.*—A suspension made from a single strain, that employed in the U. S. Army. Marketed in packages of three ampules, one containing 500 million, and two each 1,000 million killed bacteria; also in packages of three syringes, one containing 500 million, and two each 1,000 million killed bacteria.

Cutter Laboratory, Berkeley, Calif.

*Typhoid Vaccine.*—A suspension of killed bacilli in physiologic sodium chloride solution with 0.4 per cent. trikresol, containing 500 million killed typhoid bacilli of various strains in each cubic centimeter.

*Dosage:* From 5 to 50 million every three to five days.

*Typhoid Prophylactic.*—A suspension made from a single strain, viz., that employed by the U. S. Army, containing 1,000 million killed typhoid bacilli per cubic centimeter. Put up in packages of three bottles, one containing 500 million, and two each 1,000 million typhoid bacilli.

The Gilliland Laboratories, Ambler, Pa.

*Typhoid Vaccine.*—Prepared according to the method of the U. S. Army Medical School Laboratory from the Rawling's strain. Marketed in packages containing three syringes, the first containing 500 million killed typhoid bacilli and the second and third containing each 1,000 million killed typhoid bacilli; in packages containing three ampules, the first containing 500 million killed typhoid bacilli and the second and third containing each 1,000 million killed typhoid bacilli; also in ampules containing from 5 to 100 Cc. of the vaccine as ordered.

Lederle Antitoxin Laboratories, New York. (Schieffelin & Co., New York.)

*Typhoid Vaccine.*—Marketed in vials and in syringes containing respectively 100, 250, 500 and 1,000 million killed typhoid bacilli; also in 20-Cc. vials in four strengths, 1 Cc. containing respectively 100, 250, 500 and 1,000 million killed typhoid bacilli.

*Typhoid Vaccine* (For Prophylactic Treatment).—Marketed in vials and in syringes, each package containing three doses, the first dose containing 500 million killed typhoid bacilli, while the second and third dose each contain 1,000 million killed typhoid bacilli.

*Typhoid Combined Vaccine* (Prophylactic).—Marketed in vials and syringes, each package containing three doses, the first dose containing 500 million killed typhoid bacilli and 250 million killed paratyphoid bacilli A and 250 million killed paratyphoid bacilli B, while the second and third each contain 1,000 million killed typhoid bacilli and 500 million each of killed paratyphoid bacilli A and B.

Eli Lilly & Company, Indianapolis.

*Typhoid Vaccine, Prophylactic*.—Marketed in packages of one 5-Cc. and one 20-Cc. vial, each cubic centimeter containing 500 million killed typhoid bacilli; in packages of one 5-Cc. and one 20-Cc. vial, each cubic centimeter containing 1,000 million killed typhoid bacilli; in packages of three 1-Cc. vials, one containing 500 million and two each containing 1,000 million killed typhoid bacilli; in packages of three 1-Cc. syringes, one containing 500 million and two each containing 1,000 million killed typhoid bacilli. Also marketed in hospital-size packages of ten complete immunizations in thirty 1-Cc. vials.

*Typhoid Vaccine, Therapeutic*.—Marketed in packages of two 1-Cc. vials, one 5-Cc. vial and one 1-Cc. syringe, each Cc. containing 100 million killed typhoid bacilli; in packages of two 1-Cc. vials, four 1-Cc. vials, one 5-Cc. vial, one 20-Cc. vial and one 1-Cc. syringe, each cubic centimeter containing 250 million killed typhoid bacilli; in packages of two 1-Cc. vials, one 5-Cc. vial and one 1-Cc. syringe, each cubic centimeter containing 500 million killed typhoid bacilli; in packages of two 1-Cc. vials, one 1-Cc. syringe, each containing 1,000 million killed typhoid bacilli; in packages of four 1-Cc. vials, containing respectively 100, 250, 500 and 1,000 million killed typhoid bacilli; in packages of four 1-Cc. syringes, containing respectively 100, 250, 500 and 1,000 million killed typhoid bacilli.

*Typhoid Mixed Vaccine* (*Typho-Bacterin Mixed*).—Marketed in packages of three 1-Cc. vials, one containing 250 million each killed paratyphoid A and B and 500 million killed typhoid bacilli and two containing 500 million each killed paratyphoid A and B and 1,000 million killed typhoid bacilli; in packages of three 1-Cc. syringes, one containing 250 million each killed paratyphoid A and B and 500 million killed typhoid bacilli and two containing 500 million each killed paratyphoid A and B and 1,000 million killed typhoid bacilli; in packages of one 5-Cc. vial, each cubic centimeter containing 500 million each killed paratyphoid A and B and 1,000 million killed typhoid bacilli; and in one 20-Cc. vial, each cubic centimeter containing 500 million each killed paratyphoid A and B and 1,000 million killed typhoid bacilli. Also marketed in hospital-size packages of ten complete immunizations in thirty 1-Cc. vials.

H. K. Mulford Co., Philadelphia.

*Typho-Bacterin*.—Each Cc. contains about 50 million killed bacilli. Marketed in packages of four syringes (which are also sold singly), containing respectively 125, 250, 500 and 1,000 million killed typhoid bacilli; in packages of two 1-Cc. ampules, each containing 125 million killed typhoid bacilli; in packages of two 1-Cc. ampules, each containing 1,000 million killed typhoid bacilli; in 5-Cc. vials, containing 125 million killed typhoid bacilli per cubic centimeter; in 5-Cc. vials, con-



taining 1,000 million killed typhoid bacilli per cubic centimeter, and in 20-Cc. vials, containing 50 million killed typhoid bacilli per cubic centimeter.

*Typho-Bacterin (Immunizing).*—Marketed in packages of three syringes, one containing 500 million killed typhoid bacilli, while the other two each contain 1,000 million killed typhoid bacilli. The contents of these syringes should be injected subcutaneously at intervals of ten days. Also marketed in hospital-size packages of thirty ampules, in sets of three, each set being sufficient for the complete immunization of one patient.

*Typho-Bacterin Mixed (Immunizing).*—Marketed in packages of three syringes, one syringe containing 500 million killed typhoid bacilli and 250 million each of paratyphoid A and B, while the other two syringes each contain twice the number of killed bacilli contained in the first.

National Vaccine and Antitoxin Institute, Washington, D. C.

*Anti-Typhoid Vaccine (Immunizing).*—Prepared according to the technic of Russel from the strain used in the U. S. Army. Marketed in three syringes, one containing 500 million, and two each 1,000 million killed typhoid bacilli; also in ampules containing the same doses.

Parke, Davis & Co., Detroit.

*Typhoid Vaccine (Prophylactic).*—Marketed in bulbs, each bulb containing 1,000 million killed typhoid bacilli, sterilized with heat and ready for use.

C. H. Sherman, Detroit.

*Typhoid Bacillus Vaccine.*—Marketed in three strengths, containing respectively about 50, 500 and 1,000 million killed typhoid bacilli per cubic centimeter.

E. R. Squibb & Sons, New York.

*Typhoid Vaccine, Curative.*—Marketed in boxes of 4 syringes containing 100, 200, 500 and 1,000 million killed bacilli. Also in boxes of 2 syringes containing 100 and 500 million killed bacilli; boxes of 6 ampules, two containing each 100 million, two each 500 million and two each 1,000 million killed bacilli, with a syringe and boxes of two ampules containing 100 and 500 million killed bacilli, with a syringe.

*Typhoid Vaccine (Immunizing).*—Marketed in boxes of 3 syringes containing 500, 1,000 and 1,000 million killed bacilli; also in boxes of three ampules containing respectively 500, 1,000 and 1,000 million killed bacilli, with a syringe.

Swan-Myers Company, Indianapolis.

*Swan's Typhoid Bacterin (No. 44) (Prophylactic).*—Marketed in packages of three 1 Cc. vials, of which one contains 500 million, and the other two each 1,000 million killed typhoid bacilli; in packages of six 1-Cc. vials, two of which contain each 500 million, and four vials contain each 1,000 million killed typhoid bacilli; in packages (hospital) of thirty-six vials, of which twelve contain each 500 million killed typhoid bacilli and twenty-four contain each 1,000 million killed typhoid bacilli; and in packages (board of health) of seventy-two vials, of which twenty-four contain each 500 million killed typhoid bacilli and forty-eight contain each 1,000 million killed typhoid bacilli.

*Mixed Bacterial Vaccines*

These contain more than one species of bacteria.

*Actions and Uses.*—The employment of bacterial vaccines should be based either on the discovery of the causative micro-organism by careful bacteriologic examination of the case under treatment or on well established clinical knowledge which has shown the disease present to be regularly due to the activity of a definite germ. As a rule, one organism plays the predominant rôle and the destruction of the causative agent will effect a cure. In some cases, however, it has been found that two or more organisms are associated in producing the diseased condition. In such cases a vaccine containing all the known causative antigens has been thought to be indicated. When this etiologic association has been determined by actual bacteriologic examination a mixture of two autogenous vaccines or two corresponding stock vaccines may be expected to give good results. If the bacteriologic examination be omitted, the mixture rests on a purely hypothetical assumption and the method becomes wholly irrational. The temptation to add other varieties of bacteria that possibly may be present leads to the formation of complex mixtures, comparable only to the worst forms of "shotgun" treatment.

While the subject was still in the experimental stage, various mixtures of vaccine, so-called "mixed" vaccines, were admitted to N. N. R. by the Council. As knowledge concerning the action of these products increased, however, it was found inadvisable, in most instances, to continue recognition of them; and the mixed vaccines, which had been admitted, were deleted unless their usefulness was established by acceptable clinical evidence. The new mixed vaccine products are subjected to the same condition before being accepted.

In some conditions the association of bacteria is so constant as to form an apparent justification for the manufacture of stock vaccines containing a mixture of such bacteria constantly found together in certain definite conditions. These, when admitted to N. N. R., have been classified under "Mixed Bacterial Vaccines."

The Abbott Laboratories, Chicago.

*Staphylo-Acne Bacterin, Polyvalent.*—Marketed in syringes, containing respectively 275 million killed bacteria (250 million mixed staphylococci and 25 million acne bacilli) and double, quadruple and octuple these numbers; also in packages of six ampules, each containing 550 million killed bacteria (500 million staphylococci and 50 million acne bacilli).

Cutter Laboratory, Berkeley, Calif.

*Staph-Acne Vaccine.*—*Staph-Acne Bacterin.*—A mixture of killed staphylococci and of killed acne bacilli in physiologic sodium chloride

solution with 0.4 per cent. trikresol; each cubic centimeter containing 500 million staphylococci and 50 million acne bacilli.

Dosage: From 100 to 2,000 million.

H. K. Mulford Co., Philadelphia.

*Staphylo-Acne Bacterin*.—Marketed in packages of four syringes (which may also be obtained singly), the first containing 250 million killed staphylococci (*albi* and *aurei* mixed) and 25 million killed acne bacilli, and the others containing respectively two, four and eight times these quantities; in 20-Cc. vials containing 250 million killed staphylococci and 25 million killed acne bacilli per cubic centimeter; in packages of two 1-Cc. ampules, each containing 250 million killed staphylococci and 25 million killed acne bacilli; in packages of two 1-Cc. ampules, each containing 2,000 million killed staphylococci and 200 million killed acne bacilli; in 5-Cc. vials containing 250 million killed staphylococci and 25 million killed acne bacilli per cubic centimeter, and 5-Cc. vials containing 2,000 million killed staphylococci and 200 million killed acne bacilli per cubic centimeter.

E. R. Squibb & Sons, New York.

*Staphylo-Acne Vaccine*.—Marketed in boxes of 4 syringes containing 100 million killed staphylococci and 25 million killed acne bacilli, 200 million killed staphylococci and 50 million killed acne bacilli, 400 million killed staphylococci and 100 million killed acne bacilli, and 500 million killed staphylococci and 200 million killed acne bacilli; boxes of 2 syringes containing 100 million killed staphylococci and 50 million killed acne bacilli and 500 million killed staphylococci and 200 million killed acne bacilli; boxes of 2 ampules containing 100 million killed staphylococci and 50 million killed acne bacilli and 500 million killed staphylococci and 200 million killed acne bacilli, with a syringe; also in boxes of 6 ampules containing respectively 100 million killed staphylococci and 20 million killed acne bacilli, 100 million killed staphylococci and 20 million killed acne bacilli, 500 million killed staphylococci and 50 million killed acne bacilli, 500 million killed staphylococci and 50 million killed acne bacilli, 1,000 million killed staphylococci and 100 million killed acne bacilli, and 1,000 million killed staphylococci and 100 million killed acne bacilli, with a syringe.

**ERYSIPELAS AND PRODIGIOSUS TOXINS (COLEY).**—This preparation is practically a mixed bacterial vaccine made from strains of *Streptococcus pyogenes* isolated from cases of erysipelas and from *Bacillus prodigiosus*. Its use has been advised in cases of inoperable sarcoma.

*Actions and Uses.*—This remedy is said to have produced cures in 10 per cent. of the total number of cases treated. It is worthy of trial in cases in which radium or the roentgen ray is unsuccessful.

*Dosage.*—0.05 to 0.5 Cc. (1 to 8 minims). It is given by hypodermic injection partly into the tumor or its near neighborhood and partly at a distance to secure the benefit of both local and systemic effect. A reaction consisting of chill and rise of temperature is expected to follow the injections until tolerance becomes established.

Parke, Davis & Co., Detroit.

*Erysipelas and Prodigiosus Toxins* (Coley).—Marketed in 1-oz. bottles.

### *Sensitized Bacterial Vaccines—Serobacterins*

These products are prepared in the same manner as bacterial vaccines, except that the bacterial suspensions are treated with the serum of an animal which has been immunized to some extent against the species of bacterium in hand. The serum is then washed from the bacterial bodies by centrifugation and the latter are resuspended in physiologic sodium chloride solution. This treatment, it is claimed, sensitizes the bacteria so that they are more easily attacked by the protective forces of the patient, cause less reaction, and produce a quicker immunity. It is held that a time-consuming portion of the process of immunity, namely, the formation of specific amboceptors necessary for the breaking up of the bacteria, is dispensed with. These amboceptors, procured from the immunized goat and combined with the bacteria, it is believed, prepare the bacteria in the same manner as amboceptors formed in the body of the patient; their action, therefore, is much more rapid than that of the ordinary bacterial vaccine.

*Method of Preparation.*—An immune serum is obtained from goats, or other animals, which have been treated by injections of dead, and later, living cultures of bacteria until the blood shows a high titer of specific antibodies (opsonins, agglutinins, etc.). A heavy suspension of bacteria is mixed with a corresponding immune serum. The mixture is kept at laboratory temperature for twenty-four hours, with frequent shaking. During this time the bacteria and antibodies contained in the immune serum are believed to combine. Sterile saline solution is then added and the mixture centrifugated. The bacteria with the specific antibodies attached are thrown down and the supernatant fluid is removed. The washing is repeated until all traces of free serum are removed. After sensitization the bacteria are killed by heat or antiseptics.

H. K. Mulford Co., Philadelphia.

*Acne Serobacterin-Mulford (Sensitized Acne Vaccine, Polyvalent).*—Marketed in packages of four syringes containing respectively 250, 200, 400 and 800 million killed sensitized acne bacilli; in single syringes containing 800 million killed sensitized acne bacilli; in 5-Cc. vials containing 100 million killed sensitized acne bacilli per cubic centimeter, and in 5-Cc. vials containing 800 million killed sensitized acne bacilli per cubic centimeter.

*Cholera Serobacterin-Mulford (Sensitized Cholera Vaccine).*—Marketed in packages of three syringes containing respectively 500, 1,000 and 2,000 million killed sensitized cholera vibrios suspended in sterile physiologic sodium chloride solution.

*Coli Serobacterin-Mulford (Sensitized Coli Vaccine).*—Marketed in packages of four syringes containing respectively 250, 500, 1,000 and 2,000 million killed sensitized colon bacilli; in single syringes, each containing 2,000 million killed sensitized colon bacilli; in 5-Cc. vials containing 250 million killed sensitized colon bacilli per cubic centimeter,



and in 5-Cc. vials containing 2,000 million killed sensitized colon bacilli per cubic centimeter.

*Meningo-Serobacterin-Mulford (Sensitized Meningococcus Vaccine).*—Marketed in packages of three syringes, one containing 1,000 million, and the other two each 2,000 million killed sensitized meningococci.

*Neisser Serobacterin-Mulford (Sensitized Gonococcic Vaccine).*—Marketed in packages of four syringes containing respectively 250, 500, 1,000 and 2,000 million killed sensitized gonococci; in single syringes, each containing 2,000 million killed sensitized gonococci; in 5-Cc. vials containing 250 million killed sensitized gonococci per cubic centimeter and in 5-Cc. vials containing 2,000 million killed gonococci per cubic centimeter.

*Pneumo Serobacterin-Mulford (Sensitized Pneumococcic Vaccine).*—Marketed in packages of four syringes containing respectively 250, 500, 1,000 and 2,000 million killed sensitized pneumococci; in single syringes, each containing 2,000 million killed sensitized pneumococci; in 5-Cc. vials containing 250 million killed sensitized pneumococci per cubic centimeter, and in 5-Cc. vials containing 2,000 million killed sensitized pneumococci per cubic centimeter.

*Staphylo-Serobacterin-Mulford (Sensitized Staphylococcic Vaccine).*—Marketed in packages of four syringes containing respectively 500, 1,000, 2,000 and 4,000 million killed sensitized staphylococci; in single syringes, each containing 4,000 million killed sensitized staphylococci; in 5-Cc. vials containing 500 million killed sensitized staphylococci per cubic centimeter, and in 5-Cc. vials containing 4,000 million killed sensitized staphylococci per cubic centimeter (all these are composed of *S. aureus* and *S. albus* in equal quantities).

*Staphylo Acne Serobacterin-Mulford (Sensitized Staphylo Acne Vaccine).*—Marketed in packages of four syringes, the first containing 500 million killed sensitized staphylococci and 100 million killed sensitized acne bacilli, while the second, third and fourth contain, respectively, double, quadruple and octuple these quantities; two, four and eight times these quantities; in single syringes, each containing 4,000 million killed sensitized staphylococci and 800 million killed sensitized acne bacilli; in 5-Cc. vials containing 500 million killed sensitized staphylococci and 100 million killed sensitized acne bacilli per cubic centimeter, and in 5-Cc. vials, each containing 4,000 million killed sensitized staphylococci and 800 million killed sensitized acne bacilli per cubic centimeter.

*Strepto-Serobacterin-Mulford (Sensitized Streptococcic Vaccine).*—Marketed in packages of four syringes containing respectively 250, 500, 1,000 and 2,000 million killed sensitized streptococci; in single syringes, each containing 2,000 million killed sensitized streptococci; in 5-Cc. vials containing 250 million killed sensitized streptococci per cubic centimeter, and in 5-Cc. vials containing 2,000 million killed sensitized streptococci per cubic centimeter.

*Strepto-Serobacterin Scarlatinal-Mulford (Immunizing) (Sensitized Streptococcic Vaccine Scarlatinal).*—Marketed in packages of three syringes, of which one contains 1,000 million and two each 2,000 million killed streptococci.

*Strepto-Serobacterin Scarlatinal-Mulford (Therapeutic) (Sensitized Streptococcic Vaccine Scarlatinal).*—Marketed in packages of four syringes containing, respectively, 250, 500, 1,000 and 2,000 million killed sensitized streptococci; in single syringes, each containing 2,000 million killed sensitized streptococci; in 5-Cc. vials, each containing 250 million killed sensitized streptococci per cubic centimeter, and in 5-Cc. vials, each containing 2,000 million killed sensitized streptococci per cubic centimeter.

*Typho-Serobacterin-Mulford (Sensitized Typhoid Vaccine).*—Marketed in packages of four syringes containing respectively 250, 500, 1,000 and 2,000 million killed sensitized typhoid bacilli; in single syringes, each containing 2,000 million killed sensitized typhoid bacilli; in 5-Cc. vials, each containing 250 million killed sensitized typhoid bacilli per cubic centimeter; and in 5-Cc. vials, each containing 2,000 million killed sensitized typhoid bacilli per cubic centimeter.

*Typho-Serobacterin-Mulford, Mixed (Immunizing) (Sensitized Typhoid Vaccine).*—Marketed in packages of three syringes, the first containing 1,000 million killed sensitized typhoid bacilli, 500 million killed sensitized paratyphoid A and 500 million killed sensitized paratyphoid B; and the second and third containing each 2,000 million killed sensitized typhoid bacilli, 1,000 million killed sensitized paratyphoid A and 1,000 million killed sensitized paratyphoid B.

*Typho-Serobacterin-Mulford (Immunizing).*—Each package contains three syringes of typho-serobacterin graduated as follows:

Dosage: First dose, 1,000 million killed sensitized typhoid bacilli; second and third doses, 2,000 million killed sensitized typhoid bacilli each.

### III.—Diagnostic Agents

#### A.—AGGLUTINATING SERUMS FOR THE IDENTIFICATION OF BACTERIA

These serums are prepared by immunizing an animal with an undoubted strain of the specific organism until the serum yields a high content of specific agglutinins (see under Serums). The animal is then bled, the serum collected, and generally dried for better preservation.

For use, a weighed portion of the powder is dissolved and the solution added to a suspension of a pure culture of the organism in question in physiologic sodium chloride solution so as to make a dilution of the same strength as the "agglutinating titer." After from one to twenty-four hours' incubation, clumping of the organism, which may be observed by the naked eye or under the microscope, is evidence that it is the same as the one used for the preparation of the serum.

Usually a series of tubes is prepared containing different dilutions of the serum, and the highest dilution which shows definite clumping is taken as the agglutinating titer of the serum with respect to the organism in question. Control tubes, containing only the saline suspension or saline suspension with normal horse-serum, should be used to ensure that the organisms do not clump spontaneously. Other tubes, containing the serum in its given agglutinating titer and a suspension of an undoubted strain of the organism from which the serum was made, should be used to ensure the potency of the serum under the conditions of the experiment. Correct interpretation of agglutination phenomena requires considerable bacteriologic training.

H. K. Mulford Co., Philadelphia.

*Cholera Agglutinating Serum.*—The dried blood serum of horses which has been injected with killed cultures of the cholera vibrio. It is intended for the diagnosis of cholera by the agglutination of suspected cholera vibrios.

For use the serum is dissolved in salt solution so as to make a definite dilution, commonly 1:100. A drop of this is mixed with the suspected culture and the mixture is observed under the microscope for evidences of agglutination.

*Agglutinating Serum for the Identification of Bacillus Paratyphosus A.*—Marketed in sealed ampules containing each 1 Gm. of the dried serum having the agglutinating titer 1:20,000. Intended for use by the macroscopic method, the reading being taken after twenty-four hours.

*Agglutinating Serum for the Identification of Bacillus Paratyphosus B.*—Marketed in sealed ampules containing each 1 Gm. of the dried serum having the agglutinating titer 1:50,000. Intended for use by the macroscopic method, the reading being taken after twenty-four hours.

*Agglutinating Serum for the Identification of Bacillus Typhosus.*—Marketed in sealed ampules containing each 1 Gm. of the dried serum having the agglutinating titer 1:24,000. Intended for use by the macroscopic method, the reading being taken after twenty-four hours.

#### B.—WIDAL'S TEST FOR TYPHOID FEVER

This most important test depends, also, on agglutination; but the problem is reversed. The serum is unknown and the bacteria are known typhoid bacilli. The following two modifications allow the use of killed bacilli, so as to make it practically a bedside test in lieu of more exact laboratory determinations.

##### 1. BASS MODIFICATION OF THE WIDAL TEST.—

The agglutination is observed on a glass slide with the naked eye.

H. K. Mulford Co., Philadelphia.

*Bass Test for Typhoid Fever.*—The outfit consists of the following items: (a) suspension or emulsion of killed typhoid bacilli, each cubic centimeter containing approximately 10 billion killed bacilli; (b) glass slide on which to mix the emulsion with suspected blood; (c) slide with dried smear of infected blood, this slide is to be afterward used for mixing the emulsion and suspected blood on Slide B; (d) needle for pricking ear or finger to obtain suspected blood from the patient; (e) pipet for dropping typhoid emulsion and water on slide, previous to mixing with suspected blood.

**2. BORDEN'S MODIFICATION OF THE WIDAL TEST.**—In this test the serum of the blood is mixed with salt solution and then with a suspension of killed typhoid bacilli, so as to bring the dilution up to 1 to 50. The positive reaction is determined by noting that the clumps of bacilli sink to the bottom of the test tube and leave a limpid, clear fluid above a small, white, flocculent mass of agglutinated bacilli.

H. K. Mulford Co., Philadelphia.

*Mulford's Widal Test Outfit (Widal Reaction for Serodiagnosis of Typhoid Fever).*—The outfit consists of the following items, all packed in a box containing fixed test tube rack: (a) 30-Cc. stock bottle of suspension or emulsion of killed typhoid bacilli; (b) 30-Cc. stock bottle of physiologic sodium chloride solution, containing 1 per cent. of phenol; (c) 10-Cc. dropping flask for salt solution; (d) 10-Cc. dropping flask for typhoid suspension; (e) 6 graduated test tubes; (f) 1 graduated pipet; (g) 12 small capillary bulbs or tubes to collect blood serum and (h) 1 needle.

#### C.—COMPLEMENT FIXATION REACTION FOR SYPHILIS

This test depends on the presence in the blood serum of syphilitics of some immunity product, which, in the presence of an "antigen," combines with the "complement" which is present in all fresh blood, so that the "complement" is not available for a further immunity reaction.

This further immunity reaction, which is used to test the absence of uncombined or "unfixed" complement in the mixture with syphilitic blood or its presence in case the mixture has been made with nonsyphilitic blood, is the hemolytic reaction, which is performed as follows:

If an animal, such as a rabbit, be immunized by injection of human red blood cells, its serum will contain an "amboceptor" which, in the presence of "complement," will dissolve human blood cells in a test tube. This is called an antihuman hemolytic system. If sheep cells were used for immunization we should have an antisheep hemolytic system. The original Wassermann reaction for syphilis (a modification of the Bordet-Gengou complement fixation technic) used an anti-sheep hemolytic system and fetal syphilitic liver extract as antigen. The Noguchi modification uses an antihuman hemolytic system, and a lipoid extract from the heart muscle, not necessarily syphilitic. Fresh guinea-pig serum is used as complement in both cases, and tests are necessary to determine the units of complement and of amboceptor necessary barely to cause the hemolysis of a definite amount of suspension of washed blood corpuscles. Further tests of the antigen must be made to show that it will not inhibit hemolysis in itself, but will do so in the presence of known syphilitic serum. The test proper is made by incubating complement, antigen, and a fixed amount of the suspected serum for one hour; then the amboceptor and the washed corpuscles of the hemolytic system are added, and the whole is incubated again. A positive test will be indicated by absence of hemolysis, the red corpuscles having settled to the bottom and the fluid being colorless above them. Proper controls must be set up.

It is thus seen that the reaction is a complicated one, being really a series of reactions between at least five substances, successive bodies being introduced to test for the presence or



absence of others. Evidently even more skill in technic and in interpretation is required than with agglutination reactions.

**NOGUCHI MODIFICATION OF THE WASSERMANN TEST.**—The Noguchi test for syphilis is a modification and simplification of the Wassermann test and involves the use of antihuman amboceptor, a solution of "antigen" and "complement," the latter to be obtained from the blood of a guinea-pig.

*Amboceptor.*—This is obtained by injecting washed human blood corpuscles (erythrocytes) into rabbits, at intervals of from five to seven days, over a period of five or six weeks. Ten days are allowed to elapse before the last injection. The rabbits are then bled and the serum collected. Filter paper is now saturated with this serum and allowed to dry. The paper is cut in strips and set aside until wanted for use. In this form amboceptor will keep for a considerable length of time.

Amboceptor paper is standardized by measuring its specific activity. The measurement of specific activity consists in finding the amount of amboceptor necessary to cause hemolysis in 1 Cc. of suspended human red corpuscles, one drop of blood in 4 Cc. normal saline solution with 0.02 Cc. of fresh guinea-pig serum. This is incubated at a temperature of 37 C. for one hour. The quantity of paper necessary to cause hemolysis under these conditions is known as one unit. In the syphilis test two units are used.

*Antigen.*—This is made by rubbing liver or heart tissue with sand and extracting with absolute alcohol. Macerate 10 Gm. of tissue in 100 Cc. of alcohol for one week at 37 C., shaking the container every day. Filter until clear. Evaporate the filtrate. Dissolve the resulting extract in ether. Pour this solution into a large quantity of acetone. The acetone precipitates certain lipid substances which are then collected and redissolved in methyl alcohol, in ratio of 3 per cent. This constitutes the antigen solution. For use mix 1 part of this with 9 parts, 0.9 per cent. sodium chloride solution. This dilution should not cause hemolysis in an amount of 0.4 Cc., and 0.4 Cc. should not inhibit hemolysis.

H. K. Mulford Co., Philadelphia.

*Serodiagnosis of Syphilis (Noguchi System).*—The test consists of amboceptor paper and antigen in a package accompanied with full directions for use.

#### D.—LUETIN VACCINATION FOR THE DIAGNOSIS OF SYPHILIS

**LUETIN.**—Luetin is an extract of the killed cultures of several strains of *Spirochaete pallida*, the causative agent of syphilis.

*Actions and Uses.*—When injected into the skin, luetin provokes no reaction in normal individuals except a very small erythematous area at and around the point of injection. In certain cases of syphilitic infection, a reaction occurs consisting of papules which may become pustules. When the reaction takes the papular form, a large reddish indurated papule (usually from 7 to 10 mm. in diameter) makes its appearance in twenty-four to forty-eight hours and slowly increases for four or five days, after which the inflammatory process begins to recede. The color of the papule gradually becomes dark bluish red. The induration disappears within two weeks, as a rule.

In the pustular form, after the fourth or fifth day, the inflammatory process increases in intensity and the papules become vesicular and later purulent. The pustules rupture spontaneously and the defect caused by the escape of the pustular content becomes quickly covered by a crust that falls off within a few days. A small induration sometimes remains for a few weeks or often months, leaving a small keloid after healing.

In the torpid type of syphilis the site of injection fades to an almost invisible point within three to four days, so that it may be erroneously considered a negative reaction. After ten days, or even longer, the spot suddenly begins to enlarge and goes through the same stages as seen in the pustular type.

Luetin is employed for the diagnosis of syphilis. It is of use in the examination of tertiary cases but rarely gives a positive reaction in the primary cases or in untreated secondary cases. In patients who are under treatment by mercury or salvarsan, the reaction is frequently positive even in cases which fail to give a positive Wassermann reaction.

*Dosage.*—The amount of luetin to be injected for one test is 0.07 Cc. The material should be properly diluted and injected into, but not under, the skin. A site should be selected on the skin of the upper arm, cleansed and sterilized and the injection made as described.

H. K. Mulford Co., Philadelphia.

*Luetin, Mulford.*—This is supplied in a glass capillary tube provided with a special needle for the intradermal test containing sufficient for a single test, and also in packages containing sufficient for five tests, and in hospital size packages sufficient for fifty tests.

Pure cultures of several strains of the spirochete are allowed to grow for periods of six, twelve, twenty-four, and fifty days at 37 C. under anaerobic conditions. One set is cultivated in ascitic fluid containing a piece of sterile placenta, and the other in ascitic fluid agar also containing placenta. The lower portion of each solid culture in which a dense growth has occurred is cut out and the tissue removed. The agar columns which contain innumerable spirochetes are then carefully ground in a sterile mortar. The resulting thick paste is gradually diluted by adding, little by little, the fluid culture

which also contains an enormous mass of the pure organisms. The dilution is continued until the emulsion becomes perfectly liquid. The preparation is next heated to 60 C. for thirty minutes in a water-bath, and then 0.5 per cent. trikresol is added. When examined under the dark field microscope, numerous dead spirochetes per field may be seen. Cultures made from this suspension remain sterile, and with them no infection can be produced in the testicles of rabbits.

The suspension is kept in a refrigerator when not in use.

#### E.—TOXINS FOR IMMUNITY TESTS

##### DIPHTHERIA IMMUNITY TEST (SCHICK TEST).—

This test is intended to determine those persons who have not in their blood an amount of diphtheria antitoxin sufficient to render them immune to diphtheria. The test depends on the phenomenon that when a small amount of diphtheria toxin is injected intradermally into a person who has no free antitoxin in his blood, a circumscribed area of redness and infiltration from 1 to 2 cm. in diameter develops at the site of injection. Should the patient have free antitoxin in his blood, no reaction occurs. The reaction occurs in twenty-four to forty-eight hours, and is at its height in from forty-eight to seventy-two hours. It remains for from six to twelve days, is followed by slight scaling, and leaves a brownish, pigmented spot. In some persons, a pseudoreaction may occur, which may be differentiated by its earlier appearance and disappearance, and the facts that it is less circumscribed and is not followed by pigmentation.

The test is of special value for use in institutions and among groups of persons exposed to diphtheria, in order that it may be determined which individuals should be given an immunizing dose of diphtheria antitoxin.

Diphtheria toxin in dilute solutions, such as are necessary for the test, soon lose in potency.

H. K. Mulford Co., Philadelphia.

*Diphtheria Toxin Standardized (Schick Test).*—Marketed in mailing tubes each containing an intradermic capillary syringe tube filled with undiluted diphtheria toxin, a 20-Cc. vial filled with sterile physiologic sodium chloride solution for diluting the toxin before using, and a sterile intradermic needle.

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**SILK PEPTONE.**—A preparation of peptone derived from silk and standardized to a nearly uniform optical rotatory power.

*Actions, Uses and Dosage.*—Silk peptone is not employed therapeutically. It is used for the detection of peptolytic ferments either by changes in optical activity or by the precipitation of tyrosin. It is also valuable as an addition to culture mediums for the differentiation of bacteria.

For use, silk peptone is dissolved in water, or in testing stomach conditions it may be dissolved in the filtered contents. The solutions must be clear and entirely neutral; if

acid, they must be neutralized with sodium bicarbonate or magnesium oxide. If it is desired to keep a solution for some time, it should be covered with a layer of toluene.

1. *To Test for Peptolytic Ferments in the Tissues.*—A small piece of the organ to be examined is introduced into a solution of silk peptone (25 per cent.), covered with a little toluene, and placed in the incubator. After a short time, if peptolytic ferments are present, a more or less abundant separation of tyrosin crystals takes place. In a similar way liquids may be tested for peptolytic ferments by mixing the clear filtrates with the silk peptone solution.

2. *To Examine Stomach Contents for Peptolytic Ferments.*—5 Cc. of the stomach contents should be neutralized with magnesium oxide and filtered. To the filtrate 0.2 Gm. of silk peptone is added. The mixture is incubated and examined at intervals of thirty minutes for a possible separation of crystals (tyrosin). If this occurs, the presence of peptolytic ferments may be assumed; to confirm this assumption a test for tyrosin should be applied.

3. *The Optical Method.*—The material to be examined should receive the proper preliminary treatment mixed with a solution of silk peptone and placed in a polarimeter tube, covered with some toluene, and the optical rotation immediately determined. This is repeated at intervals of several hours for about two days, the mixture being placed meanwhile in the incubator. If a change in optical rotation occurs, while the control solution retains the original degree of rotation, the presence of peptolytic ferments may be assumed.

Silk peptone is prepared from silk waste as follows: The material is dried at 100 C. for forty-eight hours and then treated with from 3 to 5 times its weight of 70 per cent. sulphuric acid and allowed to stand for four days. It is then diluted with ten times its volume of water cooled by ice. The sulphuric acid is neutralized with barium hydroxide and filtered through charcoal. The residue on the filter is repeatedly stirred with warm water (25 C.) and decanted, or it may be washed thoroughly with boiling water. The filtrates are concentrated at a temperature not above 40 C. The thick liquid, which must be free from barium and sulphuric acid, is poured with constant stirring into absolute alcohol, which precipitates the silk peptone. Care must be taken that the alcohol is renewed at intervals so as to maintain the proper strength for precipitation. The yield with careful technic amounts to 20 to 30 per cent. of the product used.

Silk peptone is a white or yellowish powder, easily soluble in water, but not hygroscopic. The aqueous solution has a slight acid or amphoteric reaction. Its concentrated solutions are practically colorless and thus adapted for use in optical methods. It also possesses a high content of tyrosin.

**Seiden Peptone-Roche (Silk Peptone).**—A nonproprietary brand complying with the standards for silk peptone.

Manufactured by F. Hoffmann-LaRoche and Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York).



## SILVER PREPARATIONS

*Actions and Uses.*—Silver compounds are used in medicine to produce caustic, astringent, germicidal and antiseptic effects. The caustic effects are produced by the silver salts of mineral acids. When caustic effects are desired silver nitrate should be preferred, because the organic compounds of silver are largely or completely lacking in caustic properties. As an astringent, also, silver nitrate is the compound of choice, but it must be used in weaker solutions according to the astringency required.

The precipitant action may be objectionable, however, when purely antiseptic effects are desired; for the protein precipitation causes irritation, lessens the antiseptic efficiency and hinders penetration.

Modifications of these objectionable qualities of silver nitrate have been accomplished generally by combining silver with some form of protein. Nonprecipitant compounds are thus formed. The antiseptic efficiency is also greatly diminished and is much less than might be expected from their silver content. This can be compensated for by the use of more concentrated solutions. In practice, therefore, the organic silver compounds, in which the silver ion is not altogether masked, are fairly satisfactory antiseptics.

Silver protein compounds possess the antiseptic action of silver nitrate to some degree. They do not precipitate proteins and are relatively or entirely nonirritant. They are frequently used as substitutes for silver nitrate, especially for the prophylaxis and treatment of the sensitive mucous membranes, particularly in gonorrhea, conjunctivitis and other infections of the urethra and of the eye, ear, nose and throat.

To prepare solutions of silver protein compounds the substance is sprinkled on distilled water and allowed to dissolve; in this way the formation of lumps, which dissolve slowly, is avoided.

The argyrol type is nonirritating. The protargol type produces distinct though slight irritation.

Under certain conditions involving a very fine state of subdivision, metallic silver and some of its compounds ordinarily insoluble become capable of colloidal suspension, forming with water mixtures closely resembling solutions. (In these suspensions colloidal substances are in such extreme state of subdivision that they were formerly supposed to be in solution and are still commonly but wrongly so considered. The use in ordinary medical literature of the word "solution" referring to such suspensions should not be severely criticized, but should be eliminated as far and as soon as possible.) These preparations are not precipitated by the ordinary precipitants of silver salts. Consequently they can be mixed with organic liquids or injected into the tissues or even into the blood stream without precipitation and without

causing marked symptoms of irritation. They possess to a greater or less degree the antiseptic properties of solutions of silver.

The silver preparations may be arranged under the following types:

*Colloidal Silver Preparations of the Collargol Type.*—Containing 50 to 78 per cent. of silver in the form of metallic silver oxide or silver in colloidal state forming deeply colored solutions, turbid by reflected light, of relatively high specific gravity. This includes collargol and cargentos, electrargol is also said to contain colloidal silver, but in much smaller quantity (0.04 per cent.).

*Silver Protein Preparations of the Argyrol Type.*—Containing 20 to 25 per cent. of silver; nonirritant; forming deeply colored solutions of relatively high specific gravity. Includes: argyrol, solargentum-Squibb, and sophol.

*Silver Protein Preparations of the Protargol Type.*—Containing 7 to 8.5 per cent. of silver; slightly but distinctly irritant; solutions of lower specific gravity than the argyrol group; solutions generally less deeply colored. Includes: protargol and silver proteinate "Heyden".

*Simple Silver Salts.*—Albargin, silver citrate, silver lactate.

### Colloidal Silver Preparations

**CARGENTOS.**—*Argenti Oxidum Colloidale*-Mulford.—Colloidal Silver Oxide, Mulford.—A preparation of colloidal silver oxide with a sufficient amount of modified casein to maintain the silver oxide in colloidal form when in solution. It contains silver equivalent to 25 per cent. metallic silver.

*Actions and Uses.*—Cargentos possesses the usual antiseptic properties of the colloidal silver preparations. It is nonirritating even in 50 per cent. suspension.

It is used as a substitute for the ordinary compounds of silver in treatment of inflamed mucous membranes and as an intestinal antiseptic. It may be used in 50 per cent. colloidal suspensions for the purpose of producing a shadow in roentgenographic examinations.

*Dosage.*—For application in diseases of the eye and of the genito-urinary organs from 5 to 25 per cent. colloidal suspensions; for application to other mucous membranes from 10 to 50 per cent. colloidal suspensions may be used. Freshly made colloidal suspensions are always to be preferred.

Manufactured by the H. K. Mulford Company, Philadelphia. U. S. patent No. 1,043,646 (Nov. 5, 1912; expires 1929). No U. S. trademark.

*Cargentos Aseptic Vaginal Tampons.*—Colloidal Silver Oxide Aseptic Vaginal Tampons.—Aseptic wool tampons impregnated with 0.325 Gm. (5 grains) of cargentos. The tampons are contained in No. 10 thin gelatin capsules. A silk cord is attached to the capsule, permitting the ready removal of the wool.

*Cargentos Dusting Powder.*—Colloidal Silver Oxide Dusting Powder.—A mixture containing cargentos 10 parts, purified talcum and magnesium carbonate sufficient to make 100 parts by weight.

*Cargentos Ointment.*—Ointment of Colloidal Silver Oxide.—An ointment said to contain cargentos 1 part with anhydrous wool fat 9 parts by weight, put up in collapsible tubes.

*Cargentos Tablets.*—Colloidal Silver Oxide (3 grains)-Mulford.—Each tablet contains cargentos 0.195 Gm. (3 grains) without excipient.

To prepare a solution the tablet should be crushed and powdered, sprinkled on the required quantity of cold water, allowed to stand for about 5 minutes and then agitated until solution occurs.

*Cargentos Rectal Suppositories.*—Colloidal Silver Oxide Rectal Suppositories-Mulford.—Each suppository weighs 1.25 Gm. (19¼ grains) and contains cargentos 0.130 Gm. (2 grains) in a vehicle consisting of oil of theobroma, together with a sufficient quantity of yellow wax.

*Cargentos Vaginal Suppositories.*—Colloidal Silver Oxide Vaginal Suppositories-Mulford.—Each suppository weighs about 6.4 Gm. (98½ grains) and contains cargentos 0.325 Gm. (5 grains). The vehicle consists of oil of theobroma together with a sufficient quantity of yellow wax.

*Cargentos Urethral Suppositories.*—Colloidal Silver Oxide Urethral Suppositories or Bougies-Mulford.—Each suppository weighs about 2.5 Gm. (37 grains) and contains cargentos 0.130 Gm. (2 grains). The vehicle consists of glycerite of boroglycerin, gelatin and water.

Cargentos is prepared by precipitating an alkaline solution of silver caseinate and silver oxide by an acid, dissolving the precipitate in an alkali, dialyzing the resulting solution against running water and evaporating the remaining colloidal suspension to dryness *in vacuo*.

Cargentos occurs in odorless and tasteless black scales of metallic luster. It forms a colloidal suspension with water and glycerin. Colloidal suspensions of cargentos are reddish brown by transmitted light and greenish black by reflected light. Suspensions of cargentos should be prepared with cold water and kept in dark-colored bottles. Its colloidal suspensions are not precipitated by sodium chloride or by albumin in the secretions.

Cargentos, when assayed by the following method, should be found to contain silver equivalent to from 24 to 26 per cent. From 0.6 to 1 Gm. cargentos is weighed into a crucible and ignited gently at first, afterward with full flame and a Bunsen burner, until the ash is light in color. The residue is treated with concentrated nitric acid, and, if completely dissolved, the solution is diluted with 50 Cc. water, 2 Cc. ferric ammonium sulphate solution added and directly titrated with tenth-normal potassium sulphocyanate. If after treating with nitric acid an insoluble residue of silver chloride remains, it is collected on a filter, washed with water, dried, ignited and weighed as silver chloride; the silver content of the filtrate is determined by titration with tenth-normal sulphocyanate as before, and the silver so found is added to that obtained in the silver chloride.

**COLLARGOL.**—Collargolum.—Colloidal Silver.—Argentum Colloidale.—Argentum Credé.—An allotropic form of metallic silver, with a small percentage of albumin with products of its oxidation. It contains silver equivalent to approximately 78 per cent. metallic silver. It forms with water a fairly stable colloidal suspension.

*Actions and Uses.*—Collargol is claimed to produce increased leukocytosis.

*Dosage.*—It is employed in carefully filtered solutions (colloidal suspensions) varying in strength according to the intended use; from 10 to 20 Cc. of a 2 per cent. solution for intravenous injections; from 0.02 to 1 per cent. solution for washes. Collargol solutions should not be sterilized by boiling, but sterile solution media should be used. Locally it is used in the form of a 15 per cent. ointment (see collargol ointment) from 2 to 4 Gm. (30 to 60 grains) being very thoroughly rubbed into the skin; in the form of 5 per cent. dusting powder, prepared with finest clay; of bougies containing 0.2 Gm. (3 grains), and vaginal suppositories and tampons each containing 0.05 Gm. ( $\frac{3}{4}$  grain); for parenchymatous injections in from 0.5 to 1 per cent. glycerin solutions. Internally a solution (colloidal suspension) of from 1:500 to 1:100 is given freely in teaspoonful doses added to the food, in infectious gastric and intestinal diseases. It is also given in tablets containing 0.06 Gm. (1 grain).

Manufactured by the Heyden Chemical Works, Garfield, N. J. (Schering & Glatz, Inc., New York). U. S. trademark No. 32,452.

*Collargol Ointment.*—Unguentum Credé.—Ointment of Colloidal Silver.—Collargol ointment is an ointment containing 15 per cent. of collargol.

Collargol occurs as small, hard, brittle, bluish-black scalelike pieces; with 20 parts of distilled water it forms a colloidal suspension, black in incident light and reddish brown in transmitted light, which remains stable for months. The addition of albumin to collargol prevents or delays its precipitation by acids and salts. A sufficient amount of albumin to prevent its precipitation under ordinary conditions is, therefore, added to collargol during its manufacture. Hence collargol, even when added to spring or well-water containing salts, undergoes no change. Whereas colloidal silver containing no albumin precipitates on being boiled. Collargol solutions brought once to the boiling point present no macroscopic changes, though they do decrease in stability.

A colloidal suspension of collargol does not respond directly to the usual tests for silver. If the colloidal suspension is warmed with nitric acid a white cloudiness is produced, which clears completely on standing, and the silver can then be demonstrated in the usual manner. If a fragment of collargol is heated on a platinum scoop, shining white metallic silver of the ordinary kind, insoluble in water, is at once formed.

Its colloidal suspension should not be exposed to light, or air; it is incompatible with the usual silver reagents.

Collargol ointment is prepared by incorporating 15 parts of collargol with 5 parts of water, 10 parts of white wax, and 70 parts of benzoinated lard, taking care that the soluble silver shall not be transformed into metallic silver of the ordinary kind. This, it is asserted, it is liable to be unless great care is observed in the manipulation.

The natural color of collargol ointment is reddish brown. The ointment is good as long as it colors the skin black.



**ELECTRARGOL.**—A colloidal suspension of silver containing a small percentage of sodium arabate. It contains silver equivalent to 0.04 per cent. metallic silver (Ag).

*Actions and Uses.*—Electrargol is claimed to be antiseptic, germicidal and nonirritating even when injected hypodermically or intravenously.

It is also said to be useful when applied locally in inflammatory conditions, and it has been used in surgical cases.

*Dosage.*—Subcutaneously, intramuscularly or intravenously it is used in doses of from 5 to 25 Cc. after being made isotonic by the addition of sodium chlorid solution.

Manufactured by Comar & Cie, Paris, France (E. Fougere & Co., Inc., New York). No U. S. patent. U. S. trademark No. 105,975.

*Ampules Electrargol for Injection, 5 Cc.*—Each ampule contains electrargol 5.0 Cc. (75 minims) in the nonisotonized condition.

The package contains a solution with directions for the extemporaneous isotonization of the preparation.

*Ampules Electrargol for Injection, 10 Cc.*—Each ampule contains electrargol 10 Cc. in the nonisotonized condition.

*Electrargol for Surgical Use.*—Supplied in bottles each containing electrargol 50 Cc. (1.7 fluidounces) isotonized by sodium sulphate.

Electrargol is prepared by passing an electric current in the form of an arc between two silver electrodes in distilled water. It is made stable by the addition of sodium arabate, which is prepared by acting on acacia (gum arabic) with hydrochloric acid, precipitating the resulting arabic acid with alcohol and neutralizing the arabic acid with sodium carbonate.

Electrargol is an odorless, tasteless liquid, appearing transparent and reddish brown by transmitted light and opaque and gray by reflected light. The addition of potassium cyanide solution or of strong nitric acid yields a colorless transparent solution. The nitric acid solution yields a white turbidity on the addition of chlorids.

### Silver Protein Preparations, Argyrol Type

**ARGYROL.**—A compound of a derived protein and silver oxide, containing from 20 to 25 per cent. of silver.

*Actions and Uses.*—See general article, Silver Preparations.

*Dosage.*—It is employed in from 10 to 25 per cent., and even stronger solutions.

Manufactured by A. C. Barnes Co., Philadelphia. U. S. trademark.

The protein constituent of argyrol is said to be prepared by electrolytic decomposition of serum albumin. To this product, finely suspended in water, is added freshly precipitated, moist silver oxide and the mixture is heated under pressure until combination occurs. The liquid is then evaporated to dryness *in vacuo*. The change in the protein is in question; probably a compound of hydrolyzed protein (serum albumin) and silver oxide is formed.

Argyrol occurs in black, glistening, hygroscopic scales, freely soluble in water and glycerin, insoluble in oils and alcohol. The solution is yellowish or black, depending on concentration, and is not affected by boiling. Solutions of argyrol stain the skin.

It gives a slight cloudiness or precipitate with sodium chloride and hydrochloric acid; on addition of ferric chloride the color is discharged with formation of a white cloud. With alkali and copper sulphate it gives a slight biuret reaction. It has a slight metallic taste. Silver is recognized in the usual way.

The compound is said to be incompatible with acids and most of the neutral and acid salts in strong solution.

**SOLARGENTUM-SQUIBB.**—A compound of silver and gelatin, containing from 19 to 23 per cent. of silver in colloidal form.

*Actions and Uses.*—See general article, Silver Preparations.

*Dosage.*—Solargentum-Squibb is used in solutions containing from 1 to 25 per cent., or more. It is also used in the form of bougies or suppositories.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

Solargentum-Squibb is produced by the interaction of silver oxide and gelatin in the presence of an alkali. When combination has occurred, the solution is concentrated and dried *in vacuo*.

Solargentum-Squibb occurs in the form of black, lustrous, odorless, granules. It is very soluble in distilled water; insoluble in oils and alcohol.

No precipitate is produced when sodium chloride solution is added to an aqueous solution of solargentum-Squibb. An aqueous solution of solargentum-Squibb does not precipitate albumin; it is decomposed with precipitation by addition of free acids or ferric chloride.

To about 1 Gm. of powdered solargentum-Squibb, accurately weighed in a porcelain crucible, add a mixture of 4.5 Gm. of lead oxide and 0.5 Gm. of powdered tartaric acid. Rotate and mix in a crucible. Heat cautiously until thoroughly carbonized and then heat in a blast flame until the lead button formed is about half its original size. Allow the crucible to cool, then place it in a beaker and dissolve the lead button containing the silver in dilute nitric acid. Transfer the liquid, with washings, into an Erlenmeyer flask and titrate the silver nitrate with tenth-normal potassium sulphocyanate volumetric solution, using ferric ammonium sulphate as an indicator. The silver content corresponds to not less than 19 per cent. and not more than 23 per cent. of metallic silver (each cubic centimeter of tenth-normal potassium sulphocyanate volumetric solution is equivalent to 0.0107 Gm. silver).

**SOPHOL.**—A compound of silver and methylene-nucleinic acid, the silver being in organic ("masked") form.

*Actions and Uses.*—See general article, Silver Preparations.

*Dosage.*—Sophol may be applied in from 2 to 5 per cent. solutions; these are best made by sprinkling the powder on cold water, without stirring.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent No. 825,545 (May 7, 1907; expires 1924). U. S. trademark No. 62,900.

*Sophol Tubes, 5 gr.*—Each tube contains sophol, 5 grains.

Sophol is prepared by conversion of insoluble silver compounds of methylene nucleinic acid in soluble silver compounds by treatment with neutral salts, such as chloride of sodium. Sophol is a yellowish powder, having a metallic taste and claimed to contain silver,

equivalent to not less than 20 per cent. metallic silver. Sophol is readily soluble in water, the aqueous solution having a faint alkaline reaction; it does not give a precipitate on the addition of dilute solution of sodium hydroxide or of sodium chloride; it is insoluble in ether and alcohol.

If 0.3 Gm. sophol is heated in a test-tube decomposition occurs with the development of brownish-red pungent vapors. If the ash is treated with dilute nitric acid, the solution filtered and hydrochloric acid added, a white cheesy precipitate is formed, which dissolves in ammonia water. If 0.5 Gm. sophol is boiled with 5 Cc. of sodium hydroxide solution, the latter assumes a black color with the development of a formaldehyde odor. If 0.1 Gm. sophol is heated with 3 Cc. nitric acid, a dirty yellow precipitate is formed, disappearing on addition of an excess of ammonia-water with the formation of an orange-colored solution. A solution of 0.5 Gm. sophol in 10 Cc. water should have a faintly alkaline reaction and should not at once become turbid on the addition of sodium chloride solution. If 1.0 Gm. sophol is shaken with 10 Cc. of alcohol and filtered, the filtrate should not be changed on addition of hydrochloric acid.

### Silver Protein Preparations, Protargol Type

**PROTARGOL.**—Protein Silver Salt.—A compound of albumin and silver containing 8.3 per cent. of silver in organic combination.

*Actions and Uses.*—See general article, Silver Preparations.

*Dosage.*—From 0.25 to 1 per cent. solution in acute gonorrhea, to 5 or 10 per cent. instillations in chronic cases, in cystitis and urethritis; in solutions of 1:1,000 to 1:2,000 as irrigations. Used also in form of bougies and tampons (from 5 to 10 per cent.). Solutions are best made by sprinkling the powder on cold water, without stirring.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent expired. U. S. trademark No. 30,882.

According to the patent specification insoluble protein silver compounds, obtained by treating protein bodies with silver salt, are rendered soluble by treatment with a solution of albumoses.

Protargol is a light-brown powder, soluble in twice its weight of cold water, producing a solution which is not affected by the ordinary precipitants of silver salts, such as alkalies, sulphides, chlorides, bromides, iodides, or by heat.

Ammonium sulphide gives a dark color to the solution without precipitation. Addition of strong hydrochloric acid produces a precipitate of unchanged protargol, soluble in a large quantity of water. A solution containing sulphuric acid is not colored blue by diphenylamine. It is compatible with picric acid and picrates and with most metallic salts. It should not be exposed to light. It is precipitated by cocaine hydrochloride, but this is prevented by addition of boric acid.

**SILVER PROTEINATE "HEYDEN"**—Argentum Proteinicum "Heyden."—Said to be identical with protargol.

*Actions and Uses.*—See general article, Silver Preparations

*Dosage.*—See under protargol.

Manufactured by the Heyden Chemical Works, New York. No U. S. patent or trademark.

Silver proteinate "Heyden" must conform with tests and have the properties described under protargol.

#### Simple Silver Salts.

**ALBARGIN.**—Gelatose Silver.—Albargin is a compound of silver nitrate with gelatose, containing from 14.8 to 15 per cent. of silver.

*Actions and Uses.*—Albargin is used as a substitute for silver nitrate. Solutions of 0.1 to 0.2 per cent. are used in the treatment of gonorrhea; 1 to 2 per cent. as prophylactic; up to 10 or 20 per cent. in the eye.

Manufactured by Farbwerke, vorm. Meister, Lucius & Bruening, Höchst a. M., Germany (H. A. Metz Laboratories, Inc., New York). U. S. patent No. 681,482 (expired).

*Albargin Tablets.*—Each tablet contains albargin 0.2 Gm. (3 grains).

Albargin is prepared by adding silver nitrate to a solution of gelatose in water, evaporating the solution or precipitating the compound by the addition of ether or alcohol. It is a coarse, yellow, shining powder, very easily soluble in water, forming neutral solutions. An aqueous solution of albargin is reduced to metallic silver by pyramidon, an intermediate blue color being formed during the reaction. Tannin added to a 10 per cent. solution produces a flocculent precipitate. Albargin responds to the usual test for nitrate. It is incompatible with tannin and chlorides.

**SILVER CITRATE.**— $\text{Ag}_3\text{C}_6\text{H}_5\text{O}_7$ .—The normal silver salt of citric acid.

*Actions and Uses.*—Silver citrate is a nonirritating antiseptic.

It is said to be useful in the treatment of wounds, ulcers, gonorrhea and other diseases of mucous membranes.

*Dosage.*—It may be applied in substance to wounds. Solutions of from 1:4,000 to 1:10,000 are recommended for injection into the body cavities, the urethra, etc.

Solution of citric acid is neutralized with sodium carbonate and a solution of silver nitrate added with constant stirring. The precipitate is allowed to subside, washed with water, and dried on porous plates. The entire operation must be conducted under protection from the light.

Silver citrate forms an odorless, heavy powder which is moderately sensitive to the light. It is almost insoluble in water. Pure silver citrate when heated to redness leaves a residue of metallic silver weighing 63.16 per cent. of the original salt.

It should be carefully protected from the light.

**Silver Citrate-Merck.**—A nonproprietary preparation which on heating yields not less than 62 per cent. of metallic silver.

Merck & Co., New York, distributors.



**SILVER LACTATE.**— $\text{Ag.C}_3\text{H}_5\text{O}_3 + \text{H}_2\text{O}$ .—The normal silver salt of lactic acid.

*Actions and Uses.*—The 1:300 to 1:500 aqueous solution is said to be equal in disinfecting power to a 1:1,000 solution of mercuric chloride. It is irritating if applied in substance to wounds.

It is intended for all purposes for which a powerful antiseptic is desired.

*Dosage.*—From 1:100 to 1:2,000 solutions.

Silver lactate is prepared by dissolving freshly precipitated silver carbonate in a solution of lactic acid by the aid of heat and concentrating the solution until crystallization begins. The operation must be conducted in a darkened room.

Silver lactate occurs in the form of crystalline needles, granular masses or crystalline powder; it dissolves in about 15 parts of water. Pure silver lactate when heated leaves a residue of metallic silver weighing 50.2 per cent. It is usually colored somewhat brown and gives with water a brownish or reddish solution. The salt must be protected from the light.

**Silver Lactate-Merck.**—A nonproprietary preparation which on heating yields from 50 to 51.5 per cent. of metallic silver.

Merck & Co., New York, distributors.

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**SODIUM ACID PHOSPHATE.**—Sodii Biphosphas.—Sodium Dihydrogen Phosphate.—Sodium Biphosphate.—Monosodium Orthophosphate.—Primary Sodium Phosphate.— $\text{NaH}_2\text{PO}_4 + \text{H}_2\text{O}$ .—The monosodium dihydrogen salt of orthophosphoric acid,  $\text{H}_3\text{PO}_4$ , containing not less than 82 per cent. of anhydrous sodium acid phosphate.

*Actions and Uses.*—Sodium acid phosphate undergoes no change in the stomach. In the intestine it is converted into disodium hydrogen phosphate (secondary or neutral sodium phosphate). In large doses it produces laxative effects similar to those produced by the official disodium hydrogen phosphate (sodium phosphate U. S. P.). The neutralization of the acid phosphate is accomplished by alkali drawn from the blood. This tends to reduce the alkalinity of the system, which reduction is prevented by the excretion of acid in the urine. Sodium acid phosphate can thus be used to render the urine acid, or increase its acidity. It is used for this purpose to assist the action of hexamethylenamine which is effective only in acid urine. For this purpose sodium acid phosphate should be given long enough before the hexamethylenamine so that it may have left the stomach before the latter remedy enters it.

*Dosage.*—From 1 to 1.5 Gm. (15 to 20 grains) repeated frequently until the urine becomes acid. It may be administered in sweetened water like lemonade. It should not be prescribed in solution with hexamethylenamine.

Sodium acid phosphate occurs as large, colorless, transparent crystals or a white, granular, crystalline powder; odorless and having a cooling, saline and somewhat acid taste; slightly deliquescent. It is very soluble in water; insoluble in alcohol, ether or chloroform. At 100 C. sodium acid phosphate loses its water of hydration (13.04 per cent.); at 210 C. it is converted into disodium dihydrogen pyrophosphate ( $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$ ). At still higher temperatures it is changed into a mixture of sodium metaphosphate ( $\text{NaPO}_3$ ) and modifications of sodium metaphosphate.

An aqueous solution of sodium acid phosphate (1:20) is acid to litmus. An aqueous solution of sodium acid phosphate (1:20) yields a white, crystalline precipitate with an excess of magnesia mixture solution. With silver nitrate solution an aqueous solution of sodium acid phosphate (1:20) yields a yellow precipitate which is soluble in ammonia water and in nitric acid. If warmed with ammonium molybdate solution an aqueous solution of sodium acid phosphate (1:20) yields a yellow precipitate which is soluble in ammonia water. If 1 Gm. of sodium acid phosphate be dissolved in 20 Cc. of water and the solution neutralized by ammonia-water, not more than a slight turbidity should appear (limit of *calcium*, *aluminum*, etc.). If 1 Gm. of sodium acid phosphate be dissolved in 100 Cc. of 1 per cent. hydrochloric acid, 10 Cc. of the solution should not respond to the U. S. P. time-limit test for heavy metals. If 0.1 Gm. of sodium acid phosphate be dissolved in 10 Cc. of 10 per cent. sulphuric acid, the solution should not respond to the modified Gutzeit's test for arsenic proposed for the U. S. P. IX. If 0.1 Gm. of sodium acid phosphate be dissolved in 10 Cc. of 1 per cent. nitric acid and 1 Cc. of silver nitrate solution added, not more than a distinct opalescence should appear within one minute (limit of *chloride*). If from 1 to 2 Gm. of sodium acid phosphate be dissolved in 50 Cc. of 1 per cent. hydrochloric acid and the sulphate determined in the usual way, the weight of barium sulphate found should correspond to not more than 1 per cent. of hydrated sodium sulphate ( $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ ). If from 1 to 2 Gm. of sodium acid phosphate be dried for one hour at 60 C. and the temperature be then raised to and maintained at 100 C. until the salt ceases to lose weight, it should not lose more than 15 per cent. of the weight taken (limit of *water*). If from 1 to 2 Gm. of sodium acid phosphate be weighed, dissolved in 10 Cc. of water, 10 Cc. of a cold, saturated solution of sodium chloride added, and the solution titrated with normal potassium hydroxide, using phenolphthalein as indicator, the amount of alkali consumed should correspond to not less than 82 per cent. of anhydrous sodium acid phosphate. 1 Cc. of N/1 KOH = 0.1200 Gm. of  $\text{NaH}_2\text{PO}_4$ . If from 0.1 to 0.15 Gm. of sodium acid phosphate be weighed, dissolved in 10 Cc. of water, the solution neutralized with normal potassium hydroxide (free from chloride) using phenolphthalein as indicator, 50 Cc. of tenth-normal silver nitrate added, sufficient zinc oxide (free from chloride) added with stirring to render the mixture neutral to litmus paper, the mixture diluted to 100 Cc. with water, the mixture filtered through a dry filter, and the residual silver nitrate in 50 Cc. of the filtrate determined by titration with tenth-normal potassium sulphocyanate in the usual way, the silver nitrate consumed should correspond to at least 82 per cent. of anhydrous sodium acid phosphate. 1 Cc. of N/10  $\text{AgNO}_3$  = 0.0040 Gm.  $\text{NaH}_2\text{PO}_4$ .

**Sodium Acid Phosphate-M. C. W.**—A nonproprietary brand complying with the standards for sodium acid phosphate.

Manufactured by Mallinckrodt Chemical Works, St. Louis.

**Sodium Phosphate Monobasic-Merck.**—A nonproprietary brand complying with the standards for sodium acid phosphate.

Merck & Co., New York, distributors.

**Sodium Acid Phosphate-Squibb.**—A nonproprietary brand complying with the standards for sodium acid phosphate.

Manufactured by E. R. Squibb and Sons, New York.

**Sodium Phosphate Monobasic-P. W. R.**—A nonproprietary brand complying with the standards for sodium acid phosphate.

Manufactured by Powers-Weightman-Rosengarten Co., Philadelphia.

**SODIUM SUCCINATE, EXSICCATED.**—*Sodii Succinas Exsiccatus.*—The disodium salt of succinic acid containing not less than 95 per cent. anhydrous sodium succinate,  $\text{NaOOC} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COONa}$ .

*Actions and Uses.*—Sodium succinate is a saline cathartic. It has been claimed, on not very good evidence, that it has an antiseptic action in the biliary tract. It is claimed by some clinicians that sodium succinate is useful in combating infections of the gallbladder and biliary passages.

*Dosage.*—From 0.3 Gm. (5 grains) three or four times a day.

Exsiccated sodium succinate occurs as a white, granular, odorless powder, possessing a characteristic saline taste. It is readily soluble in water, but insoluble in alcohol, ether and chloroform. When heated it chars and burns, leaving a residue which responds to tests for sodium and carbonate.

If 10 Cc. of a 1 per cent. aqueous solution of sodium succinate be treated with 10 Cc. of diluted sulphuric acid no precipitate should form; if this solution be extracted with an equal volume of ether, the ethereal extract on evaporating should leave a white crystalline residue of succinic acid. If to 10 Cc. of a 1 per cent. aqueous solution of sodium succinate a few drops of ferric chloride solution be added a voluminous reddish brown precipitate should be formed. If 10 Cc. of a 1 per cent. aqueous solution of sodium succinate be treated with 1 Cc. of diluted nitric acid, the addition of a few drops of silver nitrate solution should produce not more than a slight opalescence. If 10 Cc. of a 1 per cent. aqueous solution of sodium succinate be treated with 1 Cc. of diluted hydrochloric acid, the addition of a few drops of barium chloride solution should produce not more than a faint turbidity within ten minutes. If 10 Cc. of a 1 per cent. aqueous solution of sodium succinate be acidified with 1 Cc. diluted hydro-

chloric acid and saturated with hydrogen sulphide no coloration or precipitate should appear. If about 0.5 Gm. sodium succinate be heated with 5 Cc. of sulphuric acid U. S. P. until dissolved, not more than a darkening but not distinct charring should be observed. If from 0.75 to 1.5 Gm. exsiccated sodium succinate be dried at from 150 to 200 C., the loss in weight should indicate the presence of not more than 4.0 per cent. moisture; when assayed by the method of the U. S. P. IX (Part II, Test No. 6) for alkali salts of organic acids, the dried residue should contain an amount of sodium carbonate equivalent to at least 99 per cent. anhydrous sodium succinate ( $\text{NaOOC} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COONa}$ ). (1 Cc. of half-normal sulphuric acid is  $\text{NaOOC} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COONa}$ ). (One Cc. of half-normal sulphuric acid is equivalent to 0.0405 Gm. pure, anhydrous sodium succinate.)

**Sodium Succinate, Exsiccated-Fairchild.**—A nonproprietary brand complying with the standards for sodium succinate, exsiccated.

Manufactured by Fairchild Bros. & Foster, New York.

**Sodium Succinate, Exsiccated-Merck.**—A nonproprietary brand complying with the standards for sodium succinate, exsiccated.

Merck & Co., New York, distributors.

**SOFOS.**—A mixture of sodium dihydrogen phosphate and sodium hydrogen carbonate (sodium bicarbonate), rendered stable by coating the particles of one of the constituents with disodium hydrogen phosphate. One part of sofes has the same phosphate value as 1.75 parts sodium phosphate, U. S. P.

*Action and Uses.*—When sofes is treated with water, sodium phosphate ( $\text{Na}_2\text{HPO}_4$ ) is formed and carbon dioxide is set free. (The reaction does not go to completion, some sodium dihydrogen phosphate remaining; but this is not considered important, as primary phosphate is also formed when sodium phosphate is taken into the acid gastric fluid.) Sofes has the physiologic action of sodium phosphate. It is claimed to have an advantage over the effervescent sodium phosphate preparations in that it is free from citrate or tartrate.

*Dosage.*—For adults, from 5 Gm. to 15 Gm. (from 1 to 4 drachms) in a glassful of water, taken before effervescence ceases.

Manufactured by the General Chemical Company, New York City. U. S. patent No. 1,037,078 (Aug. 27, 1912; expires 1929) and No. 1,150,901 (Aug. 24, 1915; expires 1932). U. S. trademark applied for.

Sofes is a white powder, having a slightly acid taste. It is permanent in dry air. On the addition of water, effervescence occurs with formation of secondary sodium phosphate and evolution of carbon dioxide. (When treated with water at room temperature, about 70 per cent. of the available carbon dioxide is liberated; when treated with human gastric fluid, about 93 per cent. of the available carbon dioxide is set free.)



*Assay.*—Dissolve about 0.5 gm. of sofos, accurately weighed, in 100 Cc. of water, and, after effervescence ceases, acidity with a small excess of hydrochloric acid. Boil the solution until the carbon dioxide is removed, cool and render ammoniacal. The phosphorus content is then determined in the usual manner, weighing as magnesium pyrophosphate. The amount of phosphate radical ( $\text{PO}_4$ ) present should not be less than 46 per cent.

## SULPHANILATES

**SULPHANILIC ACID.**—*Acidum Sulphanilicum.*—1:4= $\text{C}_6\text{H}_4(\text{NH}_2)(\text{HSO}_3)+2\text{H}_2\text{O}$ . — Para-amino-benzene-sulphonic acid.

*Uses and Dosage.*—The most important use of sulphanilic acid is in Ehrlich's diazo-reaction for typhoid urines.

Twenty-five Gm. colorless aniline are gradually added to 75 Gm. concentrated sulphuric acid in a 250-Cc. flask and the mixture warmed to from 180 to 190 C., under agitation for about three hours or until a drop of the mixture dropped into a solution of potassium hydroxide no longer gives indication of the presence of aniline. At the end of the reaction the mixture is poured into 500 Cc. cold water which precipitates the sulphanilic acid as a grayish crystalline powder; it is treated with animal charcoal and recrystallized from hot water (Hager I, p. 116).

Sulphanilic acid occurs as colorless crystals slightly soluble in water, and insoluble in alcohol and ether. It is decomposed at from 280 to 300 C. It effloresces in air. It is soluble in 182 parts water at 0 C., and in 166 parts water at 10 C. It is not altered by boiling alkali, but fusion with alkali decomposes it, yielding aniline. Chromic acid mixtures oxidize it to chinon. Permanganate oxidizes it to azo-benzene-sulphonic acid and an excess of this reagent to carbon dioxide, sulphuric acid, ammonia and oxalic acid.

The cold saturated solution is not altered by hydrogen sulphide or barium chloride, but boiling with alkali should not produce a visible change. One Gm. of the powdered acid treated with 3 Cc. stannous chloric solution should not be darkened. It should leave no residue on ignition.

**Sulphanilic Acid-Merck.**—A nonproprietary brand complying with the standards for sulphanilic acid.

Merck & Co., New York, distributors.

## SULPHOICHTHYOLATE PREPARATIONS

Preparations containing as their essential constituents salts or compounds of a mixture of acids containing sulphur and designated by the group name "sulphoichthyolic acid" are obtained from certain bituminous shales. Sulphoichthyolic acid is characterized by a high sulphur content, the sulphur existing largely in the form of sulphonates, sulphones and sulphides. The ammonium compound of this so-called sulphoichthyolic acid—first introduced as ichthyol—has been used most extensively. Compounds with sodium and other metals, with albumin, with formaldehyde, etc., have also been introduced.

*Actions and Uses.*—The current estimate of the effects of sulpho-ichthyolic acid preparations is based almost entirely on the use of ichthylol. As it is not known to what constituent or constituents of ichthylol such effects as it may have are due, the actions of ichthylol cannot be transferred to similar preparations which differ from ichthylol in their composition. The use of sulphoichthyolate preparations is still largely empirical. They are considered weakly antiseptic and mildly irritant. They penetrate the skin to some extent and are said to cause some vasoconstriction on mucous membranes. Taken internally they produce some gastrointestinal irritation, with diarrhœa, etc. Their influence on metabolism has not been determined.

They are used locally under the supposition that they will secure the absorption of swellings and effusions in contusions, burns, etc., and especially in gynecologic practice, and in various skin diseases. They have been tried internally in a great variety of conditions, but their therapeutic value in many of their suggested applications has not been fully established.

**ICHTHALBIN.**—Ichthylol Albuminate.—A compound of ichthylolsulphonic acid and albumin.

*Actions and Uses.*—The actions and uses of ichthalbin are the same as those of ichthylol, with the asserted advantage of freedom from such side effects as nausea and eructations. It is recommended for the same purposes as ichthylol.

*Dosage.*—For infants, from 0.125 to 0.3 Gm. (2 to 5 grains), in gruel; older children, from 0.65 to 1 Gm. (10 to 15 grains), mixed with scraped chocolate; adults, from 1 to 1.3 Gm. (15 to 20 grains), in chocolate tablets.

E. Bilhuber, New York, distributor. English patent No. 11,344. U. S. trademark No. 31,114.

*Ichthalbin Tablets, 5 grains.*—Each tablet contains ichthalbin 5 grains.

Ichthalbin is prepared by precipitating a solution of ichthylol and albumin with diluted sulphuric acid and removing adhering odorous oil by heating the well-washed and dried precipitate for twenty-four hours at 120 C., or by washing with alcohol, benzene, petroleum benzin, chloroform, etc.

It is an extremely fine, grayish-white powder, odorless and practically tasteless. It is insoluble in water, in the gastric juice, or in acid liquids, but completely soluble in alkaline liquids.

**ITTIOLO** — *Ammonii Sulphoichthyolicum*. — An aqueous solution, the important medicinal constituents of which are ammonium compounds containing sulphur in the form of sulphonates, sulphones and sulphides. These characteristic forms of sulphur result from the sulphonation of the tarlike distillate obtained from the bituminous shales of Giffoni Vallepiana, Italy, and containing the fossil remains of fish.

*Actions and Uses.*—See general article on sulphoichthyolate preparations above. The composition of ittiolo closely resem-

bling that of the original ichthyol, it is claimed that its actions and uses are also essentially those of ichthyol.

*Dosage.*—Since this article is claimed to be closely similar to ichthyol its dosage is probably like that of the older preparation (see N. N. R., 1918, p. 160).

Manufactured by Societa' Industrie Chimiche, Giffoni Vallepiiana, Italy (Giuseppe W. Guidi, New York, distributor).

Ittiolo is a brownish-black syrupy liquid having a characteristic empyreumatic odor and burning taste.

It is almost completely soluble in water; incompletely soluble in alcohol and ether, but almost completely soluble in a mixture of equal volumes of alcohol and ether; also soluble in a mixture of equal volumes of alcohol, water, and ether. It is miscible with glycerin.

The aqueous solution of ittiolo (1:10) is faintly acid to blue litmus. The aqueous solution (1:10) yields a greenish-black resin-like precipitate upon the addition of hydrochloric acid. This precipitate is nearly insoluble in ether; it is partially soluble in alcohol; soluble in water, but if dissolved in the latter solvent it is again precipitated by the addition of hydrochloric acid. With barium chloride test solution the aqueous solution of ittiolo (1:10) gives a brownish-black precipitate which is insoluble in diluted hydrochloric acid.

Boil an aqueous solution of ittiolo (1:10) with potassium hydroxide test solution. Ammonia is evolved.

Incinerate 1 Gm. of ittiolo. 0.14 per cent. of residue remains.

Dissolve 10 Gm. of ittiolo in 90 Cc. of water, place the solution in a glass stoppered cylinder and allow to remain undisturbed for twenty-four hours. Only a slight deposit is formed.

Ittiolo loses 51.33 per cent. of its weight when dried at 100 C.

Weigh from 5 to 6 Gm. of ittiolo into a flask, add 25 Cc. of potassium hydroxide test solution and 100 Cc. of water. Distill the mixture until no more ammonia passes over, collect the distillate in 15 Cc. of normal sulphuric acid volumetric solution to which one drop of methyl orange test solution has been added, and titrate the excess of acid with tenth-normal potassium hydroxide volumetric solution; the amount of normal sulphuric acid volumetric solution consumed corresponds to 5.16 per cent. of total ammonia ( $\text{NH}_3$ ).

Weigh from 5 to 6 Gm. of ittiolo into a beaker, add 50 Cc. of water, and 10 Cc. of a ten per cent. solution of albumin, followed by 5 portions of 5 Cc. each of diluted hydrochloric acid shaking after each addition. Make up the mixture to a volume of 500 Cc. and filter through a dry filter. Heat 200 Cc. of the filtrate to boiling, add 10 Cc. of barium chloride test solution and allow the mixture to stand for twenty-four hours. Collect the precipitate of barium sulphate, heat and weigh. The weight of barium sulphate obtained corresponds to 6.2 per cent. of ammonium sulphate.

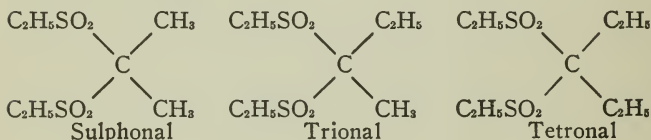
Weigh from 0.5 to 1 Gm. of ittiolo into a Kjeldahl flask, add 30 Cc. of water and 5 Gm. of potassium chlorate followed by 30 Cc. of nitric acid and evaporate the mixture to about 5 Cc.; add 25 Cc. of hydrochloric acid and evaporate to 5 Cc.; again add 25 Cc. of hydrochloric acid and evaporate to 5 Cc. Then add 100 Cc. of water, heat to boiling and add 10 Cc. of barium chloride test solution, allow the mixture to stand for twenty-four hours, collect the precipitate of barium sulphate, heat and weigh. The weight of barium sulphate corresponds to 8.87 per cent. of total sulphur. Calculate the ammonia contained in the ammonium sulphate, as previously determined in ittiolo, and subtract the result from "total ammonia" as previously determined. Multiply the remainder by the factor 1.88. The result represents the sulphur present as "sulphonic sulphur." Calculate the sulphur contained in the ammonium sulphate as previously determined in ittiolo, and subtract the result from "total sulphur" as previously determined. The remainder represents the sulphur present in the organic sulphonic acids contained in the sub-

stance. Subtract the "sulphonic sulphur" as previously calculated, from the sulphur in the organic sulphonic acids, as previously calculated. The remainder corresponds to 0.66 per cent. ("sulphide") sulphur.

Ittiolo is incompatible with acids and saline solutions, fixed alkalies, their carbonates and iodides, alkaloidal salts and mercuric chloride.

## SULPHONE METHANES

Three analogous compounds formed by the substitution of sulphone radicals in methane have been applied in therapeutics, of which sulphonethyl methyl methane or trional has been generally given the preference. These compounds have received the names sulphonal, trional and tetronal. Their chemical designations are diethylsulphone dimethyl methane, diethylsulphone methyl ethyl methane and diethylsulphone diethyl methane, corresponding to the accompanying constitutional formulas.



Of these compounds sulphonal is soluble with difficulty and slowly absorbed and its hypnotic action is but slowly established; trional is somewhat more soluble than sulphonal and acts more quickly. Both drugs are preferably given in hot liquids, and in the case of sulphonal the hypnotic effect is likely to be postponed for several hours. Sometimes it is not developed until the following day. Trional is usually effective in an hour or two.

The sulphone methanes in therapeutic doses produce sleep without noticeable effect on the circulation or respiration. In larger doses acute poisoning occurs, evidenced by disturbances of the digestive organs, the metabolism and the nervous system. When administered for too long a period cumulation is likely to occur producing a condition of chronic poisoning which terminates fatally in a large percentage of cases. In such cases hematoporphyrin derived from hemoglobin turns the urine pink or red, and this should serve as a warning, indicating the immediate withdrawal of the drug.

The symptoms of poisoning consist of persisting confusion, ataxia, constipation, vomiting, albuminuria and nephritis.

*Dosage.*—The usual dose of either sulphonal or trional is 1.0 Gm. with a maximum of 2 Gm. for sulphonal and 4 Gm. for trional. Where these drugs are used frequently the administration should be suspended once in two or three days to allow of complete elimination, and the urine should be examined frequently for hematoporphyrin.



**SULPHONMETHANE.**—Sulphonmethane is official in the United States Pharmacopeia.

*Actions, Uses and Dosage.*—See preceding general article, Sulphone Methanes.

**Sulphonal.**—A nonproprietary name applied to sulphonmethane, United States Pharmacopeia. For description see the U. S. Pharmacopeia under Sulphonmethanum. The tests of identity and purity prescribed by the United States Pharmacopeia should apply to the product dispensed under this title.

**SULPHONETHYLMETHANE.**—Sulphonethylmethane is official in the United States Pharmacopeia.

**Trional.**—A nonproprietary name applied to sulphonethylmethane, United States Pharmacopeia. For description see the U. S. Pharmacopeia under Sulphonethylmethanum. The tests of identity and purity prescribed by the United States Pharmacopeia should apply to the product dispensed under this title.

## SULPHUR COMPOUNDS

**ICHTHALBIN.**—See Sulphoichthyolate Preparations.

**THIGENOL.**—Solution of Sodium Sulpho-Oleate-Roche. —A solution of the sodium salts of synthetic sulpho-oleic acids, containing 2.85 per cent. sulphur.

*Actions and Uses.*—Thigenol is said to have the actions of sulphur. It is claimed to stimulate granulation, restrict secretions and to be antipruritic.

It is used in diseases of the uterus and its appendages and in skin diseases in which sulphur is commonly employed.

*Dosage.*—From 0.2 to 0.6 Gm. (3 to 10 grains) in plain or sweetened water. Thigenol is used locally either in the pure state or mixed in any desired proportion with ointment bases, fats or glycerin according to the intensity of action required.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York). No U. S. patent. U. S. trademark No. 51,393.

Precipitated sulphur is dissolved by boiling in the glyceride of oleic acid; the resulting solution is treated with sulphuric acid, during which process sulphurous acid escapes, and a sulpho-oleic acid is separated out. The separated sulpho-acid is then obtained by pouring into water, and subsequently washing thoroughly. By treatment with solution of sodium hydroxide, there results a solution of sodium sulpho-oleate, which is evaporated in vacuo until it has a specific gravity of from 1.05 to 1.06.

Thigenol is a dark brown liquid, having a faint sulphurous odor. It is soluble in one or more parts of water, dilute alcohol, glycerin, chloroform, oily or fatty bases, with any one of which it mixes freely. When water is the vehicle employed, it should be distilled; hard water will cause a precipitate.

Thigenol is incompatible with mineral acids or acetic acid.

## TANNIC AND GALLIC ACID DERIVATIVES

Tannic acid as such is irritating to the stomach and is largely absorbed or decomposed before reaching the intestine. The endeavor has been made, therefore, to produce such combinations of tannic acid with other substances as would be nonirritating to the stomach but would be broken up in the intestines, so that the astringent effect of tannic acid could be exerted there, where it is chiefly desired. Some of these substances are insoluble in water and acid solutions but soluble in alkalis; others, compounds of tannic acid and protein, are resistant to the gastric juice but are decomposed by the pancreatic juice, tannic acid being set free.

Tannic acid preparations were formerly much used. Of recent years they have occupied a less important position in the treatment of intestinal conditions, especially those in infancy and childhood, on account of the more intelligent management of these conditions by dietetic measures.

Gallic acid exerts no astringent action. It is, therefore, probable that its therapeutic effect on the intestines is insignificant.

### Tannic Acid Derivatives

**PROTAN.**—Tannin Nucleo-Proteid-Mulford.—A chemical combination of casein with tannic acid containing about 50 per cent. tannic acid.

*Actions and Uses.*—Protan is said to be useful as an intestinal astringent in all forms of diarrhea.

*Dosage.*—For infants and children, from 0.3 to 0.6 Gm. (5 to 10 grains) every hour; in acute catarrhal diarrhea (cholera morbus), from 1 to 2 Gm. (15 to 30 grains) every one or two hours; in chronic diarrhea, from 1.3 to 2 Gm. (20 to 30 grains) every hour or two hours.

Manufactured by the H. K. Mulford Co., Philadelphia. No U. S. patent. U. S. trademark No. 38,616.

*Friable Tablets, Protan, 2½ grains.*—Each tablet contains protan, 0.16 Gm. (2½ grains).

*Friable Tablets, Protan, 5 grains.*—Each tablet contains protan, 0.32 Gm. (5 grains).

*Friable Tablets, Protan, 7½ grains.*—Each tablet contains protan, 0.48 Gm. (7½ grains).

## TANNIC AND GALLIC ACID DERIVATIVES 325

*Protan and Opium Tablets, No. 1.*—Each tablet contains opium 0.005 Gm. ( $\frac{1}{2}$  grain) and protan 0.162 Gm. ( $2\frac{1}{2}$  grains).

*Protan and Opium Tablets, No. 2.*—Each tablet contains opium 0.03 Gm. ( $\frac{1}{2}$  grain) and protan 0.5 Gm. ( $7\frac{1}{2}$  grains).

Protan is made by adding a solution of tannic acid to an alkaline solution of casein, collecting and drying the precipitate.

It is a light brown powder, tasteless, and free from astringent action on the mouth and stomach; insoluble in water or dilute acids, and does not coagulate albumin or precipitate pepsin or peptones.

When protan is shaken with water and filtered, a colorless solution should be obtained, which should give not more than a faint trace of color with ferric chloride solution, showing absence of more than traces of free (uncombined) tannic acid. The resistance of protan to the action of the gastric juice may be shown by mixing 2 Gm. (dried at 100 C.) with 40 Cc. of 0.2 per cent. hydrochloric acid containing ten times the theoretical amount of 1:3,000 pepsin necessary to digest the protein present, warming to 40 C. for six hours, filtering off the residue, drying and weighing; from 60 to 70 per cent. of the amount taken may thus be recovered. The tannin may best be determined by difference, the casein being determined by decomposing it by the Kjeldahl-Gunning method and estimating the nitrogen.

**TANNIGEN.**—*Acidum Tannicum Diacetylicum.*—Diacetyl-Tannin.—Tannyl Acetate.— $(\text{CH}_3\text{CO})_2\text{C}_{14}\text{H}_{18}\text{O}_6$ .—The acetic acid ester of tannin.

*Actions and Uses.*—Tannigen passes unchanged into the intestine, where it becomes effective as an astringent in contact with the alkaline juice. It is therefore practically non-irritant to the stomach. (See note under Creosote and Guaiacol Compounds.)

It is employed in diarrheal affections, such as intestinal catarrhs, cholera morbus, cholera infantum and dysentery.

*Dosage.*—From 0.2 to 0.7 Gm. (3 to 10 grains) four times per day, dry on the tongue followed by a swallow of water, or mixed with food, avoiding warm or alkaline liquids.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent expired.

Tannigen is prepared by heating tannin and acetic anhydride, in molecular proportions, in the presence of glacial acetic acid in a flask under a reflux condenser, pouring the product of the reaction into water, washing the precipitate produced with warm water, drying and powdering.

It is a light-gray, almost odorless and tasteless powder, which undergoes no change when heated alone, even to 180 C., but softens when heated in water at 50 C. It is practically insoluble in cold water, scarcely soluble in hot water, but soluble in alcohol, and also in solutions of borax, sodium phosphate, sodium carbonate, lime, etc., being precipitated from these solutions by acids. It is rapidly saponified by boiling sodium or potassium hydroxide solutions, or gradually in the cold, into acetic and gallic acids, while ammonia produces acetic and tannic acids.

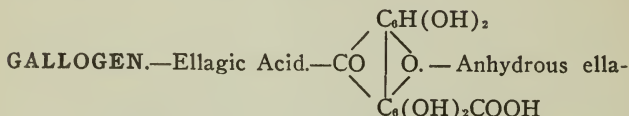
Its aqueous solutions produce with ferric salts a green color, instead of the blue-violet color characteristic of tannic acid. A slightly alka-

line solution in sodium phosphate exhibits all the characteristics of an astringent and precipitate albumin, but these properties are destroyed by borax or more alkali.

Tannigen is incompatible with alkalies and with salts of iron; it should not be exposed to heat or moisture.

### Gallic Acid Derivatives

AIROL.—See Bismuth Compounds.



gic acid prepared from divi-divi, the pods of *Caesalpinia coriaria*.

*Actions and Uses.*—Gallogen is an astringent and antidiarrheic insoluble in acid mediums and but slightly in alkaline, only slowly decomposed in the intestines, so that its astringent action extends through the whole intestinal canal.

It is used in dysentery, cholera infantum and diarrhea, even in cases of syphilitic or tuberculous origin.

*Dosage.*—From 0.3 to 0.5 Gm. (5 to 8 grains) for children; from 0.6 to 1 Gm. (10 to 15 grains) for adults, suspended in neutral or slightly acid mediums.

Manufactured by Ad. Heinemann, Eberswalde, Germany (C. Bischoff & Co., Inc., New York). German patent Nos. 137,033 and 137,034.

Gallogen is prepared by prolonged boiling of an aqueous extraction of divi-divi, whereby the amorphous acid assumes a crystalline condition and is completely precipitated, then collecting the precipitate, washing and drying.

It is a yellowish, odorless, tasteless powder, insoluble in all acid and neutral liquids, but soluble in alkaline liquids to the amount of 2 per cent., such solutions being, however, very readily oxidized.

The solutions of gallogen in alkaline mediums give all the reactions of tannic acid with iron salts, gelatin solution, etc. With fuming nitric acid it gives a characteristic dark red color.

It is incompatible with alkaline liquids.

### TERPINE DERIVATIVES

APINOL.—Apinolum.—A product obtained in the destructive distillation of the wood of *Pinus palustris* and *Pinus australis*. It is claimed to consist mainly of laevomenthone  $\text{C}_{10}\text{H}_{18}\text{O}$ .

*Actions and Uses.*—Apinol is said to be an antiseptic, germicide, local anesthetic and expectorant.

It is said to be useful when applied externally to wounds, burns, ulcers and denuded surfaces for the relief of pain and promotion of healing.



It is claimed to be of service when given internally in catarrhal inflammation of the digestive tract and, when used by inhalation, to assist in freeing the respiratory passages from accumulated mucus.

*Dosage.*—Internally from 0.3 to 1 Cc. (5 to 15 minims) with cane sugar as a menstruum.

Manufactured by the Apinol Chemical Co., Wilmington, N. C. (White Chemical Co., Wilmington, N. C.). U. S. trademark No. 29,848.

Apinol is obtained from the products of destructive distillation of pine wood. After the removal of turpentine and other low boiling constituents by distillation, the portion boiling between 182.2 and 193.3 C. is collected and purified.

It is a clear amber-colored oil with an odor resembling that of the pine, having a specific gravity of 0.946 and an approximate boiling point of 182.2 C. It is neutral in reaction.

**OIL OF PINE NEEDLES.**—*Oleum Pini.*—Oil of Pine.—*Oleum Pini Pumilionis.*—The oil distilled from the fresh leaves of *Pinus Pumilio*, Haenke.

*Actions and Uses.*—Oil of pine is employed principally as an inhalant with hot water for its stimulating and disinfecting action in catarrh of the respiratory passages, chronic laryngitis and bronchitis. It has been applied locally and given internally in the treatment of chronic rheumatic affections. When added to ether it is said to allay the irritation and diminish the bronchial secretion, which frequently become excessive, during or after the production of anesthesia by the latter drug.

*Dosage.*—From 0.05 to 0.3 Cc. (1 to 5 minims). The oil is given internally as a respiratory antiseptic and "expectorant," being taken on sugar, in capsules, or in the form of pastils. It is rubbed over rheumatic joints, which are then covered with cotton wool, or 4 Cc. (1 fluidrachm) of the oil may be added to a warm bath.

*Vapor Olei Pini.*—Oil of pine, 10 Cc.; magnesium carbonate, 5 Gm.; distilled water, sufficient to produce 100 Cc.

Mix the oil with the magnesium carbonate and add the water. A quantity sufficient for one inhalation, 4 Cc. (1 fluidrachm), is to be placed with 300 Cc. (10 fluidounces) of cold water and 300 Cc. (10 fluidounces) of boiling water in an apparatus so arranged that the air to be inhaled may pass through the solution.

Pine oil inhalation is used as a mild antiseptic in catarrhal affections of the respiratory passages.

Oil of pine occurs as a colorless or faintly yellowish liquid, having a pleasant, aromatic odor, and a pungent taste. The oil is soluble in 4.8 volumes 90 per cent. alcohol (Hager, 1908). Specific gravity, 0.865 to 0.875; begins to boil at 165 C.

It should rotate the plane of a ray of polarized light from 5° to 10° to the left at 15.5 C. in a tube 100 mm. long. Not more than 10 per cent. should distill below 165 C.

## THIOSINAMINE AND THIOSINAMINE COMPOUNDS

Thiosinamine was introduced by Hebra and Unna, 1892. It has been credited with the cure of lupus and with causing the absorption of exudates, lymphatic swellings, scar tissue, etc. The administration must be continued for weeks, and combined with massage and other adjuvant measures. It is therefore difficult to judge whether it has any value. The clinical opinions are contradictory, and no satisfactory explanation has been offered for its reputed effect. On the whole, its value, after these years of use, is not firmly established. It seems to be generally admitted that some softening of scar tissue occurs, which, however, is temporary.

Although it is usually well borne, except for the bitter taste and acid eructations, it may produce toxic systemic effects (digestive disturbance, lassitude fever; J. A. M. A., March 18, 1911, p. 835), and these may set in suddenly after it has been used for a time without toxicity. In animals, relatively small doses produce severe changes in metabolism and parenchymatous degeneration but without evidence of connective tissue changes. Larger doses impair respiration. (Tyrode: *Arch. Internat. de Pharmacod.*, **19**:195, 1910).

It is used by hypodermic injection in lupus, chronic glandular tumors, cicatrices, etc., and by the mouth in stricture, corneal opacity and chronic deafness.

Thiosinamine cannot be dissolved in water, and the alcoholic or glycerine solutions produce local irritation. Fibrolysin is a soluble compound of thiosinamine and sodium salicylate. This is practically free from the objectionable local effects.

**THIOSINAMINE.** — *Thiosinamina.* — Allyl Sulphocarbamide. — *Rhodaline.* —  $(\text{NH}_2).\text{CS}.\text{NHCH}_2.\text{CH}:\text{CH}_2$ . — Allylthiourea.

*Actions and Uses.*—See general article, Thiosinamine and Thiosinamine Compounds.

*Dosage.*—From 0.03 to 0.1 Gm. ( $\frac{1}{2}$  to  $1\frac{1}{2}$  grains) in capsules or tablet triturates; in subcutaneous injections, from 0.05 to 0.2 Gm. (1 to 5 grains) in 15 per cent. alcoholic or 10 per cent. glycerinated water solution.

Thiosinamine is prepared by warming together volatile oil of mustard (chiefly allyl thiocyanate) and alcoholic solution of ammonia, collecting the crystalline product of condensation, and recrystallizing from alcohol.

It forms colorless crystals, having a slight alliaceous odor and bitter taste and melting at 74 C. It is moderately soluble in water, but is decomposed by this solvent. It is soluble in about 3 parts of alcohol and readily soluble in ether.

Thiosinamine is incompatible with water, which decomposes it, but this change is to a limited extent prevented by the presence of glycerine.

## THORIUM SALTS AND PREPARATIONS

The soluble thorium salts bear a close resemblance to alum in their local astringent and irritant properties. They are not absorbed from the alimentary canal. Hypodermically, they cause local sloughing, and intravenously, they kill by coagulating the blood. The nonprecipitant double salts are practically nontoxic, even intravenously. They are excreted by the kidneys. Thorium salts are fairly radioactive. They have been recommended for local application in malignant diseases, and thorium emanation has been inhaled in phthisis. Reliable evidence as to other therapeutic uses of thorium salts is lacking.

**THORIUM NITRATE.**—Thorii Nitras.— $\text{Th}(\text{NO}_3)_4 + 4\text{H}_2\text{O}$ .—The thorium salt of nitric acid.

*Actions and Uses.*—See preceding general article, Thorium Salts and Preparations.

Thorium nitrate occurs as white crystalline granules or lumps. Very soluble in water and alcohol. On calcination it yields a voluminous, white oxide, which should amount to from 48 to 50 per cent. of the original salt. The aqueous solution dries over sulphuric acid to a crystalline mass.

An aqueous solution gives a white precipitate with ammonium carbonate, the precipitate being completely soluble in an excess of the precipitant. The aqueous solution gives with caustic alkalis a voluminous precipitate of the hydroxide insoluble in an excess of the precipitant. The presence of tartaric or citric acids prevents the precipitation. Potassium ferrocyanide produces an amorphous precipitate.

**THORIUM SODIUM CITRATE SOLUTION.**—A neutral, aqueous solution of thorium sodium citrate, representing thorium nitrate 10 Gm. in 100 Cc.

*Actions and Uses.*—The citrate of thorium and sodium is opaque to the Roentgen rays. It is used especially in the diagnosis of diseases of the renal pelvis and urinary bladder.

*Dosage.*—This solution is employed chiefly for cystograms. It should be sterilized by boiling before use.

According to the method of J. E. Burns (J. A. M. A., June 26, 1915, p. 2126) to make 100 Cc. of the solution, 10 Gm. of thorium nitrate are dissolved in as little distilled water as possible; to this solution, kept hot on a water or steam bath, are added 30 Cc. of a 50 per cent. solution of sodium citrate, the additions being made in small quantities and care being taken to shake the solution thoroughly after each addition. This solution is then made neutral to litmus by the careful addition of a normal solution of sodium hydroxide, and made up to 100 Cc. with distilled water. On filtration, a clear, limpid solution is obtained, which, when sterilized, either by boiling or steam under pressure, is ready for use.

**Thorium Solution for Pyelography, H. W. & D., 10 per cent.**—This solution has the composition and is prepared according to the method given for thorium sodium citrate solution.

Prepared by Hynson, Westcott & Dunning, Baltimore. No U. S. patents or trademarks.

**STRONGER THORIUM SODIUM CITRATE SOLUTION.**—A neutral, aqueous solution of thorium sodium citrate, representing thorium nitrate 15 Gm. in 100 Cc.

*Action and Uses.*—The double citrate of thorium and sodium is opaque to the roentgen rays. It is used especially in the diagnosis of diseases of the renal pelvis and urinary bladder.

*Dosage.*—This solution is employed chiefly for ureteropyelograms. It should be sterilized by boiling before use.

According to the method of J. E. Burns (J. A. M. A., June 26, 1915, p. 2126) to make 100 Cc. of the solution, 15 Gm. of thorium nitrate are dissolved in as little distilled water as possible; to this solution, kept hot on a water or steam bath, are added 45 Cc. of a 50 per cent. solution of sodium citrate, the additions being made in small quantities and care being taken to shake the solution thoroughly after each addition. This solution is then made neutral to litmus by the careful addition of a normal solution of sodium hydroxide, and made up to 100 Cc. with distilled water. On filtration, a clear, limpid solution is obtained, which, when sterilized, either by boiling or steam under pressure, is ready for use.

**Thorium Solution for Pyelography, H. W. & D., 15 per cent.**—This solution has the composition and is prepared according to the method given for stronger thorium sodium citrate solution.

Prepared by Hynson, Westcott & Dunning, Baltimore. No U. S. patents or trademarks.

## UREASE

Urease is a urealytic enzyme found in certain beans, fungi and micro-organisms.

*Actions and Uses.*—In the presence of water, urease converts urea into ammonium carbonate, thus:  $(\text{NH}_2)_2\text{CO} + 2\text{H}_2\text{O} = (\text{NH}_4)_2\text{CO}_3$ . It is employed in the determination of the amount of urea in the urine, blood and other body fluids.

*Dosage.*—For the estimation of urea in the urine, two methods are used, with various modifications: 1. A measured amount of urine is treated with urease, and after a specified time the ammonia produced is drawn into volumetric acid by means of an air current, and the residual acid deter-



mined by titration ("Absolute Method," D. D. Van Slyke: *Jour. Biol. Chem.*, 16: 125, 1913-1914). 2. The alkalinity of a portion of urine, treated with urease, is determined with volumetric hydrochloric acid (methyl orange being used as an indicator). This figure is corrected for the acidity or alkalinity of an equal volume of the same urine, determined with the same reagents. The corrected figure represents the ammonium carbonate formed by the conversion of the urea present (Marshall: *Jour. Biol. Chem.*, 14: 283, 1913).

The amount of urea in blood is determined by treating as in Method 1, the blood having been mixed as soon as drawn with potassium citrate, to prevent clotting.

**ARLCO-UREASE.**—A standardized preparation of the urealytic enzyme obtained from the jack bean, *Canavalia ensiformis*.

*Actions, Uses and Dosage.*—See preceding general article, Urease.

Manufactured by the Arlington Chemical Co., Yonkers, N. Y. No U. S. patent. U. S. trademark applied for.

In the preparation of arlco-urease, jack bean meal is treated with water and the aqueous extract filtered. The solution so obtained is precipitated by pouring into acetone, the precipitate washed and dried by desiccation over dehydrants. The dried precipitate is finely ground and standardized by methods reported by Van Slyke and Cullen. (*Proc. Soc. Exper. Biol. and Med.*, Dec. 17, 1913.)

Arlco-urease is a fine, white powder, freely soluble in water, forming an opalescent solution.

If 0.1 Gm. of arlco-urease be dissolved in 1 Cc. of water and the solution added to 5 Cc. of a 1 per cent. solution of pure urea, the mixture should hydrolyze 0.0168 Gm. of urea in fifteen minutes at 25 C. or in correspondingly less time as the temperature approaches 50 C. as a maximum.

**UREASE-DUNNING-H. W. & D.**—A standardized preparation of the urealytic enzymes obtained from the soy bean, *Soja hispida*.

*Actions, Uses and Dosage.*—See preceding general article, Urease. Urease-Dunning is supplied in the form of tablets only (see below).

Manufactured by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

*Urease-Dunning Tablets-H. W. & D.*—Each tablet contains 0.025 Gm. of urease-Dunning.

Urease-Dunning is a fine, almost white powder with little taste or odor; it is soluble in slightly alkaline water. It is practically free of the water-soluble proteins, which are precipitated by hydrochloric acid, and of proteins that are insoluble in water. Aqueous solutions deteriorate after standing a few days.

Urease-Dunning may be assayed as follows: To 5 Cc. of a 2 per cent. solution of urea, in water previously heated to from 38 to 40 C. and 25 mg. of urease-Dunning (one tablet), and keep the mixture at

the temperature stated for one hour; then add 0.05 Cc. of methyl orange test solution, and titrate with tenth-normal hydrochloric acid. From 20 to 25 Cc. should be required to neutralize it, equivalent to from 60 to 75 mg. urea.

**UREASE-SQUIBB.**—Jack bean urease.—A standardized preparation of the urealytic enzyme obtained from the jack bean, *Canavalia ensiformis*.

*Actions, Uses and Dosage.*—See preceding general article, Urease. Urease-Squibb is supplied in the form of powder and tablets.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

*Urease-Squibb Tablets*, 0.1 Gm.—Each tablet contains 0.1 Gm. urease-Squibb.

An aqueous extract of the jack bean is filtered, the clear filtrate reduced to dryness, the dry powder extracted with absolute alcohol, acetone and ether, dried, and the dry powder mixed with monopotassium sulphate and dipotassium phosphate in proportion to produce the maximum hydrolytic action and stability of the enzyme.

It is a fine, white, practically odorless and tasteless powder, which dissolves readily in cold water, forming an almost clear solution.

If 0.1 Gm. of urease-Squibb in 1 Cc. of water be added to 5 Cc. of phosphate-urea mixture (according to the "absolute method") and digested at 20 C. for fifteen minutes, it will decompose sufficient urea to liberate from 100 to 150 Cc. of fiftieth-normal ammonia by aeration.

## URETHANES (CARBAMATES), UREA AND UREIDS

The starting-point of this group is urea, which is carbamide,  $\text{NH}_2\text{CO.NH}_2$ . By the addition of a molecule of water to this compound, we have ammonium carbamate,  $\text{NH}_2\text{CO.ONH}_4$ ; substitution of ethyl for ammonium yields ethyl carbamate or urethane,  $\text{NH}_2\text{CO.O(C}_2\text{H}_5\text{)}$ , which is official in the U. S. Pharmacopeia. By substitution of phenyl for hydrogen we get  $\text{NH(C}_6\text{H}_5\text{).CO.O(C}_2\text{H}_5\text{)}$ , phenyl urethane or phenyl ethyl carbamate. By substituting for the ethyl of urethane the radical of methyl propyl carbinol we get methyl propyl carbinol urethane,  $\text{NH}_2\text{CO.O.CH(CH}_3\text{)CH}_2\text{CH}_2\text{CH}_3$ , or hedonal.

Thermodin is phenacetin urethane,  $\text{C}_6\text{H}_5\text{O.CO.N(CH}_3\text{O).C}_6\text{H}_4\text{(OC}_2\text{H}_5\text{)}$ .

Urethanes are diuretic and hypnotic agents. They are oxidized in the system to carbon dioxide and urea. Urethane is a comparatively feeble hypnotic; euphorin is used as a local anesthetic; hedonal has been employed not only as a hypnotic but also as an adjunct in the production of anesthesia, being given about an hour before beginning the use of a general anesthetic. Its action is much stronger than that of urethane. Other preparations which might be referred to

this class are: malonyl urea or barbital, and monobrom isovaleryl urea or bromural. The hypnotic effects of bromural are similar to those of veronal, but much milder.

**ADALIN.**—See Bromine Derivatives.

**BROMURAL.**—See Bromine Derivatives.

**ETHYL CARBAMATE.**—For description see the U. S. Pharmacopeia under Aethylis Carbamas.

**HEDONAL.**—Methylpropylcarbinol Urethane.—Pentan-2-ol-Urethane. —  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{O.CO.NH}_2$ .—A derivative of urethane differing from ethyl carbamate, U. S. P., in that the ethyl radical has been replaced by the radical of methylpropylcarbinol (pentan-2-ol).  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CHOH.CH}_3$ .

*Actions and Uses.*—Hedonal appears to have a greater hypnotic effect than ethyl carbamate. It is said to have no after-effects and is oxidized in the body to urea and carbon dioxide. It is employed in insomnia due to mental overwork or nervous excitement occurring in the course of neurasthenia or hysteria. It is claimed to be particularly useful preliminary to anesthesia, a hypnotic dose being given and anesthesia effected with chloroform after the patient has been asleep for an hour.

*Dosage.*—From 1 to 2 Gm. (15 to 30 grains), administered dry, followed by a swallow of water, or in wafers or capsules.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. patent No. 659,202 (expired); German patent Nos. 11,496, 120,863, 120,864, 120,865.

Hedonal is prepared by heating the secondary methylpropylcarbinol or pentan-2-ol,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CHOH.CH}_3$ , with urea nitrate under pressure (U. S. patent No. 659,202), also by other methods (German patent Nos. 120,863, 120,864, 120,865).

It is a white, crystalline powder, having a faint aromatic odor and taste, melting at 74 C., and boiling at 215 C. It dissolves in 120 parts of water at 37 C., but is more soluble at higher temperatures and is readily soluble in alcohol, ether, chloroform and other organic solvents. It is readily volatilized with the vapors of water or alcohol, and when boiled with alkalis is split up into its constituents, methylpropylcarbinol, ammonia and carbon dioxide.

When hedonal is boiled with dilute sodium hydroxide, ammonia is evolved and recognized by the odor and the usual reagents, if then an aqueous solution of iodine in potassium iodide is added, and the mixture allowed to cool, the odor of iodoform derived from the alcohol is distinctly manifested.

Hedonal is incompatible with alkalis, their carbonates and bicarbonates.

**THERMODIN.**—See Phenetidin Derivatives.

**UREA.**— $\text{CO}(\text{NH}_2)_2$ .—The diamide of carbonic acid.

*Actions and Uses.*—Urea is an active diuretic; it is rapidly eliminated and is not poisonous. It is useless in the treatment of tuberculosis, and has no important solvent action on urinary calculi. It may be employed where diuresis is indicated, though it appears irrational in primary renal disease.

*Dosage.*—From 0.5 to 4 Gm. (10 to 60 grains). Urea is given in solution, or it may be enclosed in cachets.

Urea occurs as colorless transparent prismatic crystals, almost odorless and having a cooling saline taste. It is somewhat hygroscopic. It is soluble in water (1:1), more readily in hot water; soluble in alcohol (1:7) and (1:1) in boiling alcohol. It is insoluble in ether and chloroform. It fuses at 132 C., evolving ammonia and ammonium cyanate. Kept at 150 C. for some time most of it is converted to biuret. If the temperature is raised to 170 C. the biuret evolves ammonia and is converted to cyanuric acid. Heated with water under pressure it is decomposed into ammonium carbonate. It is not alkaline, but is a weak base and though a diamide, forms salts like a monacid base; these are acid to litmus. By hydrolysis it is converted into ammonia and carbon dioxide. Nitric and oxalic acids produce precipitates when added to concentrated solutions of urea.

**Urea-Merck.**—A nonproprietary brand complying with the standards for urea.

Merck & Co., New York, distributors.

**VERONAL.**—See Diethylbarbituric Acid and Compounds.

## VALERIC ESTERS

The volatile oil of valerian contains bornyl isovalerate, to which the therapeutic effects are generally attributed. This and other esters have been introduced as substitutes for the ordinary valerian preparations. These esters have the advantage of a more agreeable odor and of being better tolerated, especially since they do not give rise to unpleasant eructations.

*Actions and Uses.*—The valeric esters share whatever sedative and antispasmodic action is possessed by valerian. They are used similarly in hysteria and other neuroses, especially those of the circulatory, digestive and central nervous systems. Their actual value depends largely on suggestion.

The following valeric esters are described in N. N. R.: amyl valerate, new-bornylval, brovalol, gynoval, validol, validol camphoratum, and valyl.

**AMYL VALERATE.**—Amylis Valeras. —  $\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{CO.O}(\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2)$ .—The isovaleric acid ester of iso-amyl alcohol.



*Actions and Uses.*—Amyl valerate has been employed in the treatment of gallstone colic. Its employment in renal colic is not satisfactory.

*Dosage.*—To relieve biliary colic, from 0.2 to 0.4 Cc. (3 to 6 minims) in capsules every half hour; or 1 Cc. (15 minims) in capsules, three times daily.

Amyl valerate is obtained by separating (by distillation) the ester which is formed when valeric acid or solution of a valerate is added to a mixture of iso-amyl alcohol and sulphuric acid and the distillate obtained, washed, dried and redistilled.

Amyl valerate is a colorless liquid, having when dilute an odor of apples. It is insoluble in water, soluble in alcohol, ether and chloroform. It boils at from 188 to 190 C. The specific gravity of pure amyl valerate is 0.858 at 15 C.

**BROMURAL.**—See Bromine Derivatives.

### Borneol Valerates

**GYNOVAL.**— $\text{CH}_3\text{CH}(\text{CH}_3).\text{CH}_2.\text{COO}.\text{C}_{10}\text{H}_{17}$ .—The iso-valeric acid ester of isoborneol.

*Actions and Uses.*—Similar to those of oil of valerian and bornyval. Gynoval is said to have been given in single doses of 4.0 Gm. to dogs without any disturbances.

*Dosage.*—From 0.25 to 0.50 Gm. (4 to 8 grains) from two to four times daily, best given after meals. These doses may be increased according to the indications. Marketed in the form of pearls only.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). No U. S. patent. U. S. trademark No. 44,069.

*Gynoval Pearls.*—Each pearl contains gynoval 0.25 Gm. (4 grains).

Gynoval is said to be prepared by the esterification of isoborneol with isovaleric acid.

It is a colorless neutral fluid of a peculiar aromatic odor and mild oleaginous taste. It is soluble with difficulty in water, but easily dissolved in alcohol, ether, acetone, chloroform, benzol and petroleum-benzene. It is stated to have a boiling point of from 132 to 138 C., under 12 mm. pressure, and a specific gravity of 0.952 to 0.957 at 15 C.

Gynoval dissolves in concentrated sulphuric acid with formation of a red-brown color and liberation of an odor of sulphurous and valeric acids. When gynoval is heated with an alcoholic solution of potassium hydroxide for several hours on a water-bath it is completely split up into its components. On diluting this saponification liquid isoborneol separates in solid form, while potassium valerate remains in solution.

### XANTHINE DERIVATIVES

*Structure and Relations.*—Caffeine, theobromine and theophylline are methyl xanthines, derived from xanthine by the introduction of two or three methyl radicals into a correspond-

ing number of  $\text{NH}_2$  groups. As these may occupy various positions in the xanthine nucleus, a considerable number of methyl xanthines exist, naturally or by synthesis, differing quantitatively in pharmacologic activity. Those named, however, are the only ones of therapeutic importance, namely, caffeine = 1:3:7 trimethylxanthine; theobromine = 3:7 dimethylxanthine; and theophylline = 1:3 dimethylxanthine.

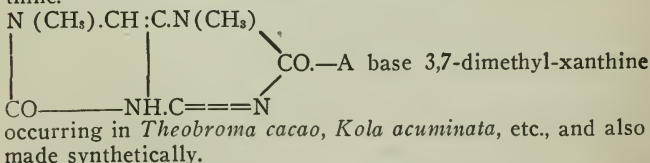
Caffeine is usually obtained from tea or coffee; theobromine is obtained from cacao or is made synthetically. Theophylline occurs in nature but in amounts too small to be commercially available; it is prepared synthetically. Theocin is a proprietary name for synthetic theophylline.

**Actions.**—Theobromine and theophylline surpass caffeine in their diuretic, and perhaps in cardiac and muscular actions. They are, therefore, generally preferred in cardiac edemas, etc., since they are equally or more effective, more prompt, and largely avoid the unpleasant side effects (insomnia, nervousness, gastric disturbance) which often interfere with the use of caffeine in adequate doses (L. B. Taylor: *Arch. Int. Med.*, December, 1914). This freedom from side effects holds particularly of theobromine. Theophylline surpasses theobromine in diuretic efficacy, but its action is probably not as lasting; it may produce gastric disturbances; renal irritation has been reported. Theobromine is, therefore, generally preferred, sometimes preceded for a few days by theophylline. If central stimulation is desired, caffeine must be used.

**Compounds.**—The slight solubility of free theobromine and theophylline limits their usefulness. They are therefore, used almost exclusively in the form of the readily soluble double salts, which they form with a considerable number of compounds. There is no reason to suppose that the particular salt used to procure the solubility has any material influence on the action. The dosage of these added compounds is also generally too small to produce therapeutic effects. It may, therefore, be assumed that the various commercial combinations are strictly equivalent.

### Theobromine and Theobromine Compounds

**THEOBROMINE.** — Theobromina. — 3,7-Dimethyl-Xanthine.—



**Actions and Uses.**—The uses of theobromine are similar to those of caffeine, but its action is said to be relatively greater

on the heart and muscles and also as a diuretic. It does not act so powerfully on the central nervous system.

It is used as a diuretic. The great obstacle to its use has been its insolubility and the consequent uncertainty of the degree of its absorption. It is liable to produce gastric disturbances.

*Dosage.*—From 0.35 to 0.5 Gm. (5 to 8 grains).

**Theobromine-Merck.**—A nonproprietary brand complying with the standards for theobromine.

Merck & Co., New York, distributors.

Theobromine is a white crystalline powder, odorless and bitterish. It is almost insoluble in cold water or chloroform; slightly soluble in hot chloroform. It forms salts with acids.

**THEOBROMINE-SODIUM ACETATE.**—*Theobrominæ Sodio-Acetas.*— $\text{NaC}_4\text{H}_7\text{N}_4\text{O}_2 + \text{NaC}_2\text{H}_3\text{O}_2$ .—A double salt of sodium acetate and theobromine-sodium.

*Actions and Uses.*—Theobromine sodium acetate acts like theobromine, over which it has the advantages of great solubility and of being well tolerated by the stomach. While inferior in diuretic power to theophyllin (which see), it is said to have greater power in sustaining the diuresis produced.

*Dosage.*—From 0.5 to 1 Gm. (8 to 15 grains), preferably in wafers or capsules. If in solution, this should be freshly prepared (with peppermint water) and without sugar or mucilage.

Theobromine sodium acetate is prepared by adding to a solution of 1 molecule of sodium hydroxide 1 molecule of theobromine. To this solution of sodium theobromine 1 molecule of sodium acetate is added and the solution brought to dryness.

It is a white, finely crystalline powder, containing 60 per cent. of theobromine. It is freely soluble in water, not very readily soluble in cold, more so in hot, alcohol. It is quite hygroscopic, and in watery solutions gradually splits up into its components, and more readily in the presence of carbon dioxide.

It is precipitated and decomposed by carbon dioxide and by acids; it forms a bluish-white precipitate with silver nitrate, a blue precipitate with copper sulphate, white with tartar emetic, red-brown with ferric salts. It is not readily precipitated by Mayer's reagent, or by iodine.

It is incompatible with carbonated beverages, acids, saccharine and mucilaginous liquids, and most of the alkaloid reagents.

**Agurin.**—A proprietary brand complying with the standards for theobromine sodium acetate.

Manufactured by Farbenfabriken, vorm. Friedr. Bayer & Co., Leverkusen, Germany (The Bayer Company, Inc., New York). U. S. trademark No. 36,018.

**Theobromine and Sodium Acetate-Roche.**—A non-proprietary brand complying with the standards for theobromine sodium acetate.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York).

**THEPHORIN.**—**Theobrominæ Sodio-Formas.**—Theobromine Sodium Formate.— $\text{NaC}_7\text{H}_7\text{O}_2\text{N}_4 + \text{NaCHO}_2 + \text{H}_2\text{O}$ .—A double salt of sodium formate and theobromine sodium.

*Actions and Uses.*—Thephorin is said not to irritate the stomach and acts as a powerful diuretic, both on account of the theobromine which it contains and also from the action of sodium formate.

It is said to be useful in cardiac affections, nephritis, dropsy, etc.

*Dosage.*—0.5 Gm. ( $7\frac{1}{2}$  grains) two or three times a day in the form of powder or as tablets.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (The Hoffmann-LaRoche Chemical Works, New York). U. S. patent No. 799,764 (Sept. 19, 1905; expires 1922). U. S. trademark No. 59,581.

*Thephorin Tablets,  $7\frac{1}{2}$  grains.*—Each tablet contains thephorin 0.5 Gm. ( $7\frac{1}{2}$  grains).

Thephorin is prepared by dissolving 70.1 parts of theobromine sodium in 200 parts of water and adding to it a solution of 23.5 parts of anhydrous sodium formate in 50 parts of water, filtering the mixture, and evaporating to dryness on a steam-bath or *in vacuo*.

Thephorin is a white, odorless powder having a saline bitter taste and is readily soluble in water producing an alkaline solution. From its aqueous solution the theobromine is precipitated by acetic acid. In the filtrate formic acid is indicated by the reduction of silver nitrate.

If an aqueous solution of thephorin be faintly acidulated with nitric acid, the filtrate should give no precipitate with barium chloride, or with silver nitrate, or with ammonia water and hydrogen sulphide. Two Gm. thephorin are placed in a porcelain dish and dissolved in 10 Cc. water with the aid of gentle heat. A few drops of phenolphthalein test solution are placed in the solution, neutralized with nitric acid, the faint alkaline reaction is again restored by means of diluted ammonia, the solution is then thoroughly stirred and, with frequent stirring, allowed to stand for three hours at ordinary temperature. The resulting precipitate collected on a weighed filter of 8 Cm. diameter is dried at a temperature of 100 C.; it is then washed twice with cold water, using 10 Cc. each time. The filter is again dried at a temperature of 100 C. and weighed. The weight of the precipitate should amount to 1.2 Gm.

### Theophyllin and Theophyllin Compounds

**THEOPHYLLIN.**—For description see the U. S. Pharmacopeia under Theophyllina.

**THEOPHYLLIN SODIO-ACETATE.**—**Theophyllinæ Sodio-Acetas.**— $\text{NaC}_7\text{H}_7\text{O}_2\text{N}_4 + \text{NaC}_2\text{H}_3\text{O}_2 + \text{H}_2\text{O}$ .—A double



salt of sodium acetate and 1.3-dimethylxanthine-sodium (theophyllinsodium).

*Dosage.*—From 0.2 to 0.35 Gm. (3 to 5 grains), best given after meals.

It is a white crystalline powder, containing about 60 per cent. of anhydrous theophyllin. It dissolves in about 20 parts of water at 25 C., but is insoluble in alcohol or ether.

## YEAST PREPARATIONS

Yeast and preparations from it are used in medicine both externally and internally. Fermenting liquids, if concentrated enough, have a bactericidal action and the value of yeast mixtures for external use is supposed to depend on this. Their internal use is based on their supposed splitting action on certain carbohydrates.

Yeast as commonly understood is the ordinary brewers' yeast, consisting of the minute unicellular organism *Saccharomyces cerevisiae*, the cells of which have a diameter of from 6 to 10 microns. These cells are characterized by their power of converting certain sugars into alcohol and carbon dioxide, which action is shown through a wide range of temperature. The active agent in this fermentation is the enzyme known as zymase. Besides the zymase, yeast contains invertase, which splits the sugars known as disaccharides into monosaccharides. In commercial mixtures there may be other ferments present as well.

Yeast grows best on a substratum of saccharine liquid containing various organic and inorganic additions, such, for example, as are found in malted grain or malt extracts. For commercial purposes it is so prepared, and a solid product, the so-called dry yeast or the compressed yeast, is obtained by filtering and completely or partially drying the collected yeast cells. Dry yeast in which there is a large addition of starchy substance retains its activity for a long time. The compressed yeast, the form commonly used in medicine, will retain its activity for several days at a low temperature.

*Actions and Uses.*—The various uses of yeast in medicine depend on the presence of several ferments. Commercial yeast is far from being a pure culture and some of the observed effects are doubtless due to the liberation of lactic acid. It has been administered in rather large doses in diabetes, and in some instances success has been attributed to such treatment. The rationale of this treatment, however, has never been satisfactorily established. Yeast has also been used as a bactericide in the treatment of external infections; here the effect may be due to the production of acids as well as of alcohol. Sugars and other carbohydrates are abundantly present in the crude yeast.

Extracts of yeast have been prepared which exhibit some of the same actions. In these the cellular structures are absent.

Concentrated liquid extracts of yeast have long been used as substitutes for meat extracts in making bouillons and soup stocks, and it is claimed that meat extract is sometimes adulterated with yeast.

**XERASE.**—A mixture of a specially prepared dry beer yeast 150 parts, grape-sugar (dextrose) 20 parts, white bole 125 parts and a mixture of nutritive salts 3 parts.

*Actions and Uses.*—This mixture is absorbent on account of the bole and readily induces fermentation, which is favored by the sugar and salts, and it is claimed that the yeast has a bactericidal action on such organisms as the gonococcus. It is said to adhere readily to mucous membranes.

It is claimed that this mixture is useful in inflammations and ulcerations of the vaginal and cervical mucous membranes and in the treatment of putrid wounds, ulcers, inoperable carcinoma, etc. It may be applied as a powder by insufflation or inserted into the vagina in a gelatin capsule.

Manufactured by J. D. Riedel, Aktiengesellschaft, Berlin, Germany (Riedel & Co., New York). No U. S. patent. U. S. trademark No. 81,482.

Xerase is a yellowish-gray powder, having a weak odor of yeast and a salty taste. It is only slightly soluble in water. It resists ordinary atmospheric conditions.

## ZINC COMPOUNDS

The essential action of salts of zinc, like those of copper and lead, is that of an astringent and corrosive. This action being largely proportional to the concentration, zinc chloride in strong solution has been used as an escharotic, fairly strong solutions of zinc sulphate as an emetic, weaker solutions of zinc sulphate and zinc acetate as astringent and antiseptic applications to the mucous membranes of the eye, urethra, etc., while the insoluble zinc oxide is used externally as a mild antiseptic and astringent. Zinc oxide was thought to act on the nervous system, but this theory is probably incorrect and the internal use of zinc oxide has been practically abandoned.

Various zinc salts containing therapeutically active acid radicals or anions have been used in medicine; thus in zinc permanganate the oxidizing action of the permanganate radical is influenced beneficially, it is claimed, by the astringent action of the zinc. Zinc peroxide is described under Metallic Peroxides.

**SOLOID NIZIN.**—Tablets, each of which contains 0.13 Gm. (2 grains) of zinc sulphanilate,  $Zn(C_6H_4(NH_2)SO_3)_2 + 4H_2O$ .

*Actions and Uses.*—Soloid nizin is an astringent and antiseptic used in gonorrhea and in conjunctivitis and other eye affections. In concentrations up to 0.4 per cent. (3 tablets per ounce) it causes practically no smarting or irritation even on the conjunctiva.

*Dosage.*—From one to three tablets in 30 Cc. (one fluid-ounce) of water for urethral injections. One tablet in 60 Cc. (2 fluidounces) for an eye-lotion.

Prepared by Burroughs Wellcome & Co., London, England, and New York. U. S. trademark No. 287,163.

**ZINC PERMANGANATE.** — *Zinci Permanganas.* —  $\text{Zn}(\text{MnO}_4)_2 \cdot 6\text{H}_2\text{O}$ .—The zinc salt of permanganic acid. It should contain not less than 90 per cent. of zinc permanganate.

*Actions and Uses.*—Zinc permanganate resembles the potassium salt in its oxidizing properties, but is more astringent. It is antiseptic. It is used chiefly in urethritis, either as an injection or as a urethral douche.

*Dosage.*—Locally 1 part to 4,000 (1 grain in 8 fluidounces). 1.3 Gm. zinc permanganate is equal in permanganate content to 1 Gm. potassium permanganate.

*"Soloid" Zinc Permanganate, 1/8 grain, B. W. & Co.*—Each tablet contains zinc permanganate 0.088 Gm. (1 1/8 grain). Prepared by Burroughs Wellcome & Co., London and New York.

*Tablets Zinc Permanganate, 1 grain, Mulford.*—Each tablet contains zinc permanganate 0.065 Gm. (1 grain). Prepared by the H. K. Mulford Co., Philadelphia.

Zinc permanganate occurs in dark brown, nearly black, lustrous deliquescent crystals, or crystalline masses. It is readily soluble in water (1:3), generally leaving a slight residue. Aqueous solutions decompose in air, but are permanent if kept in well-closed bottles, protected from light. When heated slowly it loses water of crystallization (25.46 per cent.) and oxygen, leaving a residue of zinc manganite. If heated quickly it gives off pink vapors, or more properly, a fine dust of manganese trioxid. Zinc permanganate gives up oxygen more easily than does the potassium salt, hence great care should be taken in bringing it in contact with easily oxidizable substances.

Zinc permanganate should be almost completely soluble in water. The color of the solution is discharged by alcohol, hydrogen sulphide, ferrous sulphate, oxalic acid, or hydrogen dioxid, especially if the solution is first rendered acid with sulphuric acid.

If 1 Gm. of the salt is dissolved in 50 Cc. of water and 5 Cc. of alcohol added, a colorless solution must be obtained after boiling and filtering; if a small part of the latter acidified with nitric acid is tested with silver nitrate test solution for chloride and with barium chloride test solution for sulphate, not more than traces of either should be indicated.

If zinc permanganate be examined by the method given below the residual titration should indicate the presence of not less than 90 per cent. zinc permanganate ( $\text{Zn}(\text{MnO}_4)_2 \cdot 6\text{H}_2\text{O}$ ). 0.1 to 0.2 Gm. of substance is weighed, dissolved in water, filtered through asbestos, the filtrate acidulated with 5 Cc. dilute sulphuric acid warmed to about 60

C., treated with an excess of tenth-normal oxalic acid volumetric solution, and the excess of oxalic acid determined by titration with tenth-normal potassium permanganate volumetric solution. Each cubic centimeter of tenth-normal oxalic acid volumetric solution consumed indicates 0.00411 Gm. zinc permanganate,  $\text{Zn}(\text{MnO}_4)_2 + 6\text{H}_2\text{O}$ .

**Zinc Permanganate-P. W. R.**—A nonproprietary brand complying with the standards for zinc permanganate.

Manufactured by the Powers-Weightman-Rosengarten Co., Philadelphia.

**Zinc Permanganate-Merck.**—A nonproprietary brand complying with the standards for zinc permanganate.

Merck & Co., New York, distributors.

**ZINC PEROXIDE.**—See Peroxides, Metallic.



## APPENDIX

This is an index to the proprietary articles, arranged under the names of the manufacturers or their agents, which, so far as known to the Council, comply with the rules, but which did not possess sufficient originality to be admitted to the body of the book (see Introduction to Official Rules of the Council).

Borcherdt Malt Extract Co., Chicago.

*Borcherdt's Dri-Malt Soup Extract.*—A mixture obtained by adding potassium carbonate 1.1 Gm. to each 100 Gm. of Borcherdt's Malt Extract, diluted with one half its volume of distilled water, evaporating in vacuo, and drying to a powder by a special drying process. Each 100 Gm. contains maltose, 71.10, dextrin, 13.50, protein, 8.66, salts, 2.94, and moisture, 3.80. U. S. trademark No. 64,467.

*Borcherdt's Dri-Malt Soup Extract with Wheat Flour.*—A powder obtained by evaporating to dryness by a special process a mixture of 100 Gm. of Borcherdt's Malt Soup Extract and 50 Gm. of wheat flour previously made into a paste by boiling with water. U. S. trademark No. 64,467.

*Borcherdt's Finished Malt Soup Powder.*—A powder obtained by evaporating to dryness by a special drying process a mixture of 100 Gm. of Borcherdt's Malt Soup Extract and 50 Gm. of wheat flour made into a paste by boiling with water, and 330 Gm. of milk. U. S. trademark No. 64,467.

*Borcherdt's Malt Extract with Cod Liver Oil.*—A liquid stated to be composed of cod liver oil 20 per cent. and Borcherdt's Malt Extract Plain, 80 per cent.

*Borcherdt's Malt Extract with Creosote.*—Each 100 Cc. is stated to contain beechwood creosote 0.83 Cc. (4 minims per fluidounce) in Borcherdt's Malt Extract Plain.

*Borcherdt's Malt Extract with Cascara Sagrada.*—Each 100 Cc. is stated to represent cascara sagrada 12.5 Gm. (60 grains per fluidounce) in Borcherdt's Malt Extract Plain.

*Borcherdt's Malt Extract Plain.*—A preparation essentially equivalent to Extractum Malti U. S. P. and containing 10 per cent. of glycerin. U. S. trademark Nos. 64,467, 64,481.

*Borcherdt's Malt Soup Extract.*—Borcherdt's Malt Soup Extract is a mixture obtained by adding potassium carbonate 1.1 Gm. to each 100 Gm. of Borcherdt's Malt Extract, according to the formula of Dr. Kellar, Universitäts-Kinderklinik, Breslau, Germany. U. S. trademark No. 64,467.

Burroughs Wellcome Co., New York.

*Enule Soap Compound.*—A cocoa butter suppository weighing 2.52 Gm. (39 grains) and containing in each suppository curd soap and dry sodium sulphate 0.454 Gm. (7 grains) of each.

Hynson, Westcott & Dunning, Baltimore, Md.

*Mercury Biniodide, Oil Solution in Ampuls, H. W. & D.*—One Cc. of solution contains red mercuric iodide 0.01 Gm. ( $\frac{1}{16}$  grain) in a neutral fatty oil. Each ampules contains more than 1 Cc.

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*Arsphenamine Suspension in Ampuls, H. W. & D.*—Arsphenamine (Salvarsan brand) is suspended in a mixture of vegetable fats, which are solid at 34.4 C. (94 F.), but liquid at body temperature. 1 Cc. of suspension contains 0.10 Gm. (1½ grains) of arsphenamine. Each ampule contains more than 1 Cc.

*Dosage.*—The ampule is immersed in warm water until the fat becomes liquefied, agitated, opened and the contents injected through a 20 gage needle. This preparation should not be injected intravenously.

Johnson & Co., Mead, Evansville, Ind.

*Mead's Dry Malt Soup Stock.*—A mixture containing desiccated maltose and desiccated dextrin (about equal parts), 47 per cent., wheat flour, 47 per cent., potassium carbonate, 1 per cent. and moisture, 5 per cent. U. S. patent No. 1,171,724 (Feb. 15, 1916; expires 1933).

Kalle Color & Chemical Co., New York.

*Menthol-Iodol.*—A mixture of iodol, 99 parts, and menthol, 1 part. Trademarked in Germany. No U. S. patent or trademark.

The Maltine Company, Brooklyn, N. Y.

*Maltine.*—A preparation essentially equivalent to Extractum Malti U. S. P. and containing 3.88 per cent. alcohol. U. S. trademark No. 44,556.

*Maltine with Cascara Sagrada.*—Each 100 Cc. is said to represent cascara sagrada (*Rhamnus purshiana*) 12.5 Gm. (60 grains in a fluidounce) in a mixture containing maltine 96.115 per cent. and alcohol 3.885 per cent.

*Maltine with Cod Liver Oil.*—A liquid said to represent maltine, 56.115 per cent.; cod-liver oil, 30 per cent.; alcohol, 3.885 per cent.

*Maltine with Creosote.*—Each 100 Cc. is said to represent beechwood creosote, 0.83 Cc. (4 minims in a fluidounce) in a mixture containing maltine, 96.115 per cent., and alcohol, 3.885 per cent.

*Maltine Ferrated.*—Each 100 Cc. is said to represent iron pyrophosphate, 1.65 Gm. (8 grains in a fluidounce) in a menstruum containing maltine, 96.115 per cent., and alcohol, 3.885 per cent.

*Maltine Malt Soup Extract.*—Maltine containing potassium carbonate, 1.1 Gm. to each 100 Gm. according to the formula of Dr. Keller, Universitäts-Kinderklinik, Breslau, Germany, and alcohol, 3.88 per cent.

*Maltine with Wine of Pepsin.*—A liquid said to consist of maltine, 27.5 per cent.; wine of pepsin, 71.5 per cent., and fluid extract of gentian, 1 per cent., the percentage of alcohol in the mixture being 18 per cent.

*Malto-Yerbine.*—A liquid said to contain in each 100 Cc. an extract of 6.6 Gm. (30 grains in a fluidounce) of eriodictyon (*yerba santa*), also flavoring composed of the essential oils of anise, cassia, coriander and caraway in a mixture containing maltine, 96.115 per cent., and alcohol, 3.885 per cent.

The extract of yerba santa employed in malto-yerbine is prepared as follows:

The leaves of yerba santa in coarse powder are boiled under pressure for six hours and inert matter separated by a filter press. The filtrate is concentrated with a certain quantity of maltine at a high temperature until the product has reached a density of 1.35. This extract is mixed in proper proportions with maltine of extra diastasic strength to make up for the diastasic strength lost through heat during the concentration of the drug with maltine.

Manhattan Eye Salve Co., Owensboro, Ky.

*Argyrol Ointment* (M. E. S. Co.).—An ointment said to consist of argyrol 10 per cent.; hydrous wool fat, 25 per cent.; white petrolatum, 65 per cent. Put up in collapsible tubes, for application to the eye.

*Compound Yellow Oxide and Adrenalin Ointment* (M. E. S. Co.).—An ointment said to contain yellow oxide of mercury 1 per cent., solution of adrenalin chloride 5 per cent., menthol 0.04 per cent., phenol 0.2 per cent., hydrous wool fat 25 per cent., white petrolatum sufficient to make 100 per cent. Put up in collapsible tubes, for application to the eye.

*Dionin Ointment* (M. E. S. Co.).—An ointment said to consist of dionin 5 per cent.; white petrolatum, 95 per cent. Put up in collapsible tubes, for application to the eye.

*Holocain and Adrenalin Ointment* (M. E. S. Co.).—An ointment said to consist of holocain 1 per cent.; adrenalin chloride, 4 per cent.; hydrous wool fat, 10 per cent.; white petrolatum, 85 per cent. Put up in collapsible tubes, for application to the eye.

H. K. Mulford Co., Philadelphia, Pa.

*Granular Effervescent Sodium Sulphate* (Glauber's salt)-Mulford.—A mixture said to contain in each 100 Gm.: dried sodium sulphate, 40 Gm., with an effervescing mixture consisting of sodium bicarbonate, citric acid, tartaric acid and sugar.

*Granular Effervescent Caffeine and Sodium Bromide Compound*-Mulford.—A mixture said to contain in each 100 Gm.: sodium bromide, 5.45 Gm.; caffeine, 0.545 Gm., and saccharin, 0.014 Gm., with an effervescent base consisting of sodium bicarbonate and citric and tartaric acids.

*Granular Effervescent Caffeine and Potassium Bromide*-Mulford.—A mixture said to contain in each 100 Gm.: potassium bromide, 2.3 Gm.; caffeine, 0.122 Gm., and saccharin, 0.014 Gm., with an effervescent mixture consisting of sodium bicarbonate and citric and tartaric acids.

*Granular Effervescent Carlsbad Salt (Artificial)*-Mulford.—A mixture said to contain in each 100 Gm.: potassium sulphate, 0.35 Gm.; sodium chloride, 3.266 Gm.; sodium bicarbonate, 6.533 Gm., and sodium sulphate (dried), 8 Gm., with an effervescent base consisting of sodium bicarbonate and citric and tartaric acids.

*Granular Effervescent Salicylos. — Pulvis Salicylatum Effervescens*-Mulford.—A mixture said to contain in each 100 Gm.: strontium salicylate, 6.54 Gm. (24 grains per ounce); ammonium salicylate, 6.54 Gm. (24 grains per ounce), with an effervescent base consisting of sodium bicarbonate and citric and tartaric acids.

*Lozenges Adrenal Comp.*—Lozenges each containing suprarenal gland 0.01 Gm. (1/6 grain); menthol, 0.0013 Gm. (1/50 grain); benzoic acid, 0.0026 Gm. (1/24 grain); eucalyptol, 0.0013 Gm. (1/50 grain), together with sufficient powdered sugar.

*Ointment Cargentos and Ichthyol.*—An ointment consisting of cargentos (colloidal silver oxide) 5 per cent. and ichthyol 5 per cent. in a base consisting of petrolatum, with a small amount of yellow wax.

*Rectal Suppositories Adrenal.*—Suppositories each containing dried suprarenal gland 0.3 Gm. (5 grains), together with oil of theobroma and wax.

*Syrup of Quinine with Chocolate*.—Each 100 Cc. contains in suspension: quinine sulphate, 2.156 Gm. (10 grains in a fluidounce); chloroform as a preservative 0.43 Cc. (2 minims in a fluidounce), in a syrup flavored with yerba santa, chocolate and vanillin.

National Pharmacy Co., Oakland, Calif.

*Bismuthal*.—A milky liquid, said to contain in 100 Cc.: Lac bismuthi citratis, 44 Cc.; pepsin, 3.30 Gm.; hydrochloric acid, 0.013 Gm.; lactic acid, 0.013 Gm.; glycerin, 40 Gm., and alcohol, 5 Cc.; cherry laurel water, 1.66 Cc.; Jamaica ginger, 0.26 Gm.; gum benzoin, 0.59 Gm.

Lac bismuthi citratis contains 7.60 per cent. of anhydrous bismuth citrate.

Pitman-Moore Co., Indianapolis, Ind.

*Oleum Ricini Dulce*-P. M. Co.—Castor oil to which has been added saccharin 0.07 Gm. in 100 Cc. (0.33 in a fluidounce) and aromatics; contains 2.5 per cent. alcohol.

Sargents Drug Store, Chicago.

*Petroagar*.—Each 100 grams contains petrolatum, 72 gm., agar, 22 Gm., with powdered licorice, cocoa and oil of anise sufficient to flavor. U. S. trademark applied for.

*Petrobran*.—Each 100 grams contains petrolatum, 74 gm., bran, 22 Gm., with powdered licorice and "oil of pineapple" (ethyl butyrate) sufficient to flavor. U. S. trademark applied for.

E. R. Squibb & Sons, New York.

*Ampuls Mercury Iodide Red, 1 Per Cent. in Oil-Squibb*.—A dosage form of mercuric iodide, U. S. P. Each ampule contains 1 Cc. of a solution of red mercuric iodide and anesthesin, each 0.01 Gm. ( $\frac{1}{16}$  grain) in a neutral fatty oil.

*Tablets Sodium Chloride and Citrate-Squibb (Dr. Martin H. Fischer)*.—Each tablet contains sodium chloride 1 Gm. and sodium citrate 2 Gm.

Tappan Zee Surgical Co., Nyack, N. Y.

*Causticks (Silver Nitrate 75 per cent.)*.—Wooden sticks  $1\frac{1}{2}$  inches long, tipped with a mixture of silver nitrate 75 per cent. and potassium nitrate 25 per cent., packed in amber glass bottles. Each stick is to be used but once.

*Caustick Applicators and Caustick Applicators, Special (Silver Nitrate 75 per cent.)*.—Wooden sticks  $6\frac{1}{2}$  and 12 inches long, respectively, tipped with a mixture of silver nitrate 75 per cent. and potassium nitrate 25 per cent., packed in amber glass bottles. They are intended for use in throat and gynecologic work. Each stick is to be used but once.

*Cupricsticks (Copper Sulphate 20-25 per cent.)*.—Wooden sticks  $1\frac{1}{2}$  inches long, tipped with a mixture containing from 20 to 25 per cent. of copper sulphate, alum and potassium nitrate, packed in gelatin tubes. Each stick is to be used but once.

*Cupric Applicators and Cupric Applicators, Special (Copper Sulphate 20-25 per cent.)*.—Wooden sticks  $6\frac{1}{2}$  and 12 inches long, respectively, tipped with a mixture of copper sulphate, alum and potassium nitrate, containing from 20 to 25 per cent. of copper sulphate, packed in flint tubes. Each stick is to be used but once.



*Iodosticks (Iodine 60 per cent. and Potassium Iodide 40 per cent.).*—Wooden sticks  $1\frac{1}{2}$  inches long, tipped with a mixture of iodine 60 per cent. and potassium iodide 40 per cent., package in amber glass containers. Each stick is to be used but once.

*Iodoapplicators and Iodoapplicators, Special (Iodine 60 per cent. and Potassium Iodide 40 per cent.).*—Wooden sticks  $6\frac{1}{2}$  and 12 inches long, respectively, tipped with a mixture of iodine 60 per cent. and potassium iodide 40 per cent., packed in amber glass tubes. Each stick is to be used but once.

*Stypsticks (Alum 75 per cent.).*—Wooden sticks  $1\frac{1}{2}$  inches long, tipped with a mixture of alum 75 per cent. and potassium nitrate 25 per cent., packed in gelatin tubes. Each stick is to be used but once.

*Stypstick Applicators and Stypstick Applicators, Special (Alum 75 per cent. potassium nitrate 25 per cent.).*—Wooden sticks  $6\frac{1}{2}$  and 12 inches long, respectively, tipped with a mixture of alum 75 per cent. and potassium nitrate 25 per cent., packed in glass tubes. Each stick is to be used but once.

Western Chemical Company, Inc., Hutchinson, Minn.

*Tabellae Dulces Heroin (Western) 1/100 Gr.*—Each tablet contains heroin,  $\frac{1}{100}$  grain, with cocoa, sugar and saccharine as vehicles.

*Tabellae Dulces Novaspirin (Western)  $\frac{1}{4}$  Gr.*—Each tablet contains novaspirin,  $\frac{1}{4}$  grain, with sugar, starch, liquid petrolatum, saccharine, curcuma and oil of lemon as vehicles.

*Tabellae Dulces Tannalbin (Western) 1 Gr.*—Each tablet contains tannalbin, 1 grain, with cocoa, sugar and saccharine as vehicles.

*Tabellae Dulces Terpin Hydrate with Heroin (Western)  $\frac{1}{100}$  Gr.*—Each tablet contains terpin hydrate,  $\frac{1}{2}$  grain, and heroin,  $\frac{1}{100}$  grain, with cocoa, sugar and saccharine as vehicles.



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